Efficacy and Safety of Abrilumab in a Randomized, Placebo-Controlled Trial for Moderate-to-Severe Ulcerative Colitis

Sandborn, William J ; Cyrille, Marcoli ; Hansen, Mark Berner ; Feagan, Brian G ; Loftus, Edward V ; Rogler, Gerhard ; Vermeire, Severine ; Cruz, Martha L ; Yang, Jun ; Boedigheimer, Michael J ; Abuqayyas, Lubna ; Evangelista, Christine M ; Sullivan, Barbara A ; Reinisch, Walter

Abstract: BACKGROUND AIMS: The 4 7 integrin is a validated target in inflammatory bowel disease. This randomized, phase 2b, placebo-controlled, double-blind study evaluated the efficacy and safety of the anti- 4 7 antibody abrilumab in patients with moderate-to-severe ulcerative colitis despite treatment with conventional therapies. METHODS: Patients (total Mayo Score 6-12, recto-sigmoidoscopy score 2) with inadequate response or intolerance to conventional therapies were randomized to receive subcutaneous abrilumab (7, 21, or 70 mg) on day 1, weeks 2 and 4, and every 4 weeks; abrilumab 210 mg on day 1; or placebo. The primary end point was remission (total Mayo Score 2 points, no individual sub-score >1 point) for the 2 highest dosages at week 8. Key secondary end points were response and mucosal healing (centrally read) at week 8. RESULTS: For 354 patients who received 1 dose of investigational product (placebo, n = 116; 7 mg, n = 21; 21 mg, n = 40; 70 mg, n = 98; 210 mg, n = 79), non-adjusted remission rates at week 8 were 4.3%, 13.3%, and 12.7% for the placebo and abrilumab 70-mg and 210-mg groups, respectively (P < .05 for 70 and 210 mg vs placebo); odds of achieving remission were significantly greater with abrilumab 70 mg (odds ratio 3.35; 90% CI 1.41-7.95; P = .021) and 210 mg (odds ratio 3.33; 90% confidence interval 1.34-8.26; P = .030) than with placebo. Response and mucosal healing rates with these dosages also were significantly greater than with placebo. Higher baseline 4 7 levels on naïve CD4+ T cells were a prognostic indicator for overall outcome, but not a predictive biomarker of abrilumab response. There were no cases of progressive multifocal leukoencephalopathy or deaths. CONCLUSIONS: Abrilumab treatment for 8 weeks induced remission, clinical response, and mucosal healing in patients with moderate-to-severe ulcerative colitis. ClinicalTrials.gov, number NCT01694485.

DOI: https://doi.org/10.1053/j.gastro.2018.11.035

Sandborn, William J; Cyrille, Marcoli; Hansen, Mark Berner; Feagan, Brian G; Loftus, Edward V; Rogler, Gerhard; Vermeire, Severine; Cruz, Martha L; Yang, Jun; Boedigheimer, Michael J; Abuqayyas, Lubna; Evangelista, Christine M; Sullivan, Barbara A; Reinisch, Walter (2019). Efficacy and Safety of Abrilumab in a Randomized, Placebo-Controlled Trial for Moderate-to-Severe Ulcerative Colitis. Gastroenterology, 156(4):946-957.e18.
DOI: https://doi.org/10.1053/j.gastro.2018.11.035

Gastroenterology 2019;156:946–957

Efficacy and Safety of Abrilumab in a Randomized, Placebo-Controlled Trial for Moderate-to-Severe Ulcerative Colitis

William J. Sandborn,[1] Marcoli Cyrille,[2] Mark Berner Hansen,[3] Brian G. Feagan,[4] Edward V. Loftus Jr,[5] Gerhard Rogler,[6] Severine Vermeire,[7] Martha L. Cruz,[2] Jun Yang,[2] Michael J. Boedigheimer,[2] Lubna Abuqayyas,[2] Christine M. Evangelista,[2] Barbara A. Sullivan,[2] and Walter Reinisch[8]

[1]University of California San Diego and UC San Diego Health System, La Jolla, California; [2]Amgen Inc, Thousand Oaks, California; [3]Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; [4]Robarts Clinical Trials, Western University, London, Ontario, Canada; [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [6]Department of Gastroenterology and Hepatology, University Hospital of Zurich, Zurich, Switzerland; [7]University Hospitals Leuven, Leuven, Belgium; and [8]University of Vienna, Vienna, Austria

CLINICAL AT

See Covering the Cover synopsis on page 827.

BACKGROUND & AIMS: The $\alpha_4\beta_7$ integrin is a validated target in inflammatory bowel disease. This randomized, phase 2b, placebo-controlled, double-blind study evaluated the efficacy and safety of the anti-$\alpha_4\beta_7$ antibody abrilumab in patients with moderate-to-severe ulcerative colitis despite treatment with conventional therapies. **METHODS:** Patients (total Mayo Score 6–12, recto-sigmoidoscopy score $\geq$2) with inadequate response or intolerance to conventional therapies were randomized to receive subcutaneous abrilumab (7, 21, or 70 mg) on day 1, weeks 2 and 4, and every 4 weeks; abrilumab 210 mg on day 1; or placebo. The primary end point was remission (total Mayo Score $\leq$2 points, no individual sub-score $>$1 point) for the 2 highest dosages at week 8. Key secondary end points were response and mucosal healing (centrally read) at week 8. **RESULTS:** For 354 patients who received $\geq$1 dose of investigational product (placebo, n = 116; 7 mg, n = 21; 21 mg, n = 40; 70 mg, n = 98; 210 mg, n = 79), non-adjusted remission rates at week 8 were 4.3%, 13.3%, and 12.7% for the placebo and abrilumab 70-mg and 210-mg groups, respectively ($P < .05$ for 70 and 210 mg vs placebo); odds of achieving remission were significantly greater with abrilumab 70 mg (odds ratio 3.35; 90% CI 1.41–7.95; $P = .021$) and 210 mg (odds ratio 3.33; 90% confidence interval 1.34–8.26; $P = .030$) than with placebo. Response and mucosal healing rates with these dosages also were significantly greater than with placebo. Higher baseline $\alpha_4\beta_7$ levels on naïve $CD4^+$ T cells were a prognostic indicator for overall outcome, but not a predictive biomarker of abrilumab response. There were no cases of progressive multifocal leukoencephalopathy or deaths. **CONCLUSIONS:** Abrilumab treatment for 8 weeks induced remission, clinical response, and mucosal healing in patients with moderate-to-severe ulcerative colitis. ClinicalTrials.gov, number NCT01694485.

Keywords: Ulcerative Colitis; Abrilumab; $\alpha_4\beta_7$.

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease of the colon.[1–3] Treatment of UC includes medical management and colectomy.[3–5] Goals of therapy include inducing and maintaining clinical and endoscopic remission, improving quality of life, decreasing the need for long-term corticosteroid therapy, and minimizing cancer risk.[6] Patients with moderate-to-severe UC are usually treated with oral corticosteroids; immunomodulators, such as azathioprine and 6-mercaptopurine; and biologics, including tumor necrosis factor (TNF) antagonists[2,7] or the integrin antagonist vedolizumab.[7] Despite advances in treatment, many patients with UC do not achieve symptomatic and endoscopic remission and ultimately might require colectomy.[7] Therefore, there is an unmet need for drugs with improved benefit–risk profiles and other modes of action to treat moderate-to-severe UC.

The influx of immune cells into gut mucosa, mediated through integrin-dependent leukocyte tethering, rolling, and arrest, plays an important role in inflammatory bowel disease pathogenesis.[8] The cellular adhesion molecule $\alpha_4\beta_7$ integrin is a member of the integrin family that mediates stable adhesion to high endothelial venules through the mucosal addressin cell adhesion molecule-1 and promotes migration of lymphocytes across the endothelial wall.[9] The $\alpha_4\beta_7$ integrin is expressed on circulating lymphocytes, particularly on a subset of $CD4^+CD45RA^-$ memory T cells.[10,11] Restricting homing of lymphocytes to the gastrointestinal tract, by blocking essential integrin-mediated interactions, has been an area of intensive clinical research over the past 2 decades. Selective targeting of gut lymphocyte trafficking by inhibiting the $\alpha_4\beta_7$ pathway was achieved in patients with UC and Crohn's disease with intravenously administered vedolizumab, which was approved by the US

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; CRP, C-reactive protein; FCP, fecal calprotectin; IP, investigational product; IPIM, investigational product instruction manual; NRI, nonresponder imputation; OR, odds ratio; PK, pharmacokinetic; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2018.11.035

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Despite the available treatment options, many patients with ulcerative colitis (UC) do not respond to therapy. Therefore, there is a need for new UC therapies.

NEW FINDINGS

Abrilumab, an anti-$\alpha4\beta7$ antibody treatment, for 8 weeks resulted in significantly greater remission, response, and mucosal healing rates versus placebo. Higher baseline $\alpha4\beta7$ on naïve CD4+ T cells predicted overall outcome.

LIMITATIONS

A systematic misalignment in randomization resulted in some patients receiving the incorrect dose; power to detect treatment differences was maintained. This short-term study did not fully assess treatment effects beyond 8 weeks.

IMPACT

Abrilumab is an effective treatment for UC. The data also confirm the targeting of the $\alpha4\beta7$ pathway for UC treatment.

Food and Drug Administration for induction and maintenance therapy in these indications.[12] Therefore, targeting gut-selective lymphocyte trafficking is a promising therapeutic strategy in inflammatory bowel disease.[13]

Abrilumab is a human monoclonal immunoglobulin G2 antibody that selectively targets $\alpha_4\beta_7$ and blocks interaction with mucosal addressin cell adhesion molecule-1.[14] Abrilumab is extensively absorbed after subcutaneous (SC) dosing with high bioavailability (82%–99%) and a long half-life (~31 days).[15] Receptor occupancy data from healthy individuals and 4 patients with UC showed repeated dosing of abrilumab ≥21 mg or a single dose of 210 mg resulted in near maximal receptor occupancy on peripheral blood-naïve $CD4^+$ T lymphocytes.[15] Abrilumab is formulated for SC administration, which could confer a practical advantage for patients over intravenous infusion. In this phase 2 study, we evaluated the efficacy, safety, pharmacokinetics (PK), pharmacodynamics, and receptor occupancy of abrilumab in patients with moderate-to-severe UC.

Methods

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, phase 2 induction and sustained remission trial evaluated patients with active moderate-to-severe UC who did not respond or no longer responded to conventional therapies (NCT01694485). Patient enrollment began on November 16, 2012, and data were collected through October 26, 2015, at 92 centers in North America, Europe, and Australia. The independent ethics committee or institutional review board at each center reviewed and approved the study protocol. All patients provided written and informed consent before participation. The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice regulations and guidelines. All authors had access to study data and reviewed and approved the final manuscript.

Study Design

The study consisted of a screening period (minimum 7 and up to 30 days) to establish patient eligibility followed by a 24-week, placebo-controlled, double-blind treatment period (Supplementary Figure 1). At the end of the double-blind period (week 24), patients could enter an open-label period of 108 weeks. Patients were eligible to enter the open-label period of the study early if they did not achieve a response at week 8 and had an inadequate response at week 12 or later or if they experienced disease worsening after achieving response and/or remission at week 8. Failure to achieve response at week 8 was defined as failure to achieve a decrease from baseline in total Mayo Score ≥3 points and ≥30% decrease from baseline. Inadequate response at week 12 or later was defined as failure to achieve a 2-point decrease and 25% improvement in partial Mayo Score compared with screening and minimum partial Mayo Score ≥5 points. Disease worsening was defined as an increase in partial Mayo Score ≥3 points from the week-8 value and minimum partial Mayo Score ≥5 points with recto-sigmoidoscopy sub-score ≥2.

Patients were planned to be randomized in a 2:1:2:2:2 ratio to SC placebo or abrilumab at 7 mg, 21 mg, 70 mg (on day 1, week 2, week 4, and every 4 weeks thereafter until week 24), or 210 mg (on day 1 followed by placebo in weeks 2 and 4 and every 4 weeks thereafter until week 24), respectively. Patients who progressed to the open-label phase of the study received SC abrilumab 210 mg once every 3 months. Additional details about dosing are presented in the Supplemental Materials. Assignment to treatment groups was based on a computer-generated randomization schedule. The randomization schedule was generated using a permuted block design within each stratum based on prior TNF antagonist use and participation in the PK sub-study to guarantee comparability of compared groups in the PK sub-study and had no influence on the main study. Prior TNF antagonist use was allowed in a maximum of 50% of patients enrolled in the study. Some members of the sponsor not part of the study team were unblinded to treatment allocation during the primary analysis (when all patients completed the week-12 visit or discontinued); all patients, investigators, and sponsor study team members remained blinded through the end of the double-blind period.

Study Population

Patients 18–65 years of age with moderate-to-severe active UC confirmed histopathologically and endoscopically (total Mayo Score 6–12 and centrally read [Robarts, Clinical Trials; London, Canada] Mayo endoscopic sub-score ≥2 before baseline) who exhibited inadequate or loss of response or intolerance to immunosuppressants, TNF antagonists, and/or corticosteroids (excluding patients in the United States) were eligible. Patients also were required to be free of clinically significant and unexplained neurologic signs and symptoms during screening and before randomization.

Concomitant medications deemed necessary to provide adequate supportive care were allowed during the study. Concurrent use of stable doses of 5-aminosalicylic acid and/or oral prednisone or equivalent up to 20 mg/day was permitted

in patients taking those medications for ≥2 weeks before baseline. Oral corticosteroid dose was stable through week 12; for patients in remission at week 8, the dose was decreased by 2.5 mg/week until discontinuation, while the patient was in symptomatic remission. The 5-aminosalicylic acid dosage was kept stable from day 1 through week 24; acetylsalicylic acid–based enemas were not allowed during this period. Concurrent use of azathioprine or 6-mercaptopurine was permitted if treatment was initiated ≥12 weeks before baseline and had been at a stable dosage for ≥8 weeks before baseline. Simultaneous treatment with methotrexate up to a stable dosage of 25 mg/week was permitted in patients who took the medication for ≥8 weeks before baseline. Immunomodulators were administered at stable dosages through week 8 and were withdrawn at the week-8 study visit.

Patients were excluded from the study if they met any of the following exclusion criteria: disease limited to the rectum; toxic megacolon; Crohn's disease; history of subtotal or total colectomy; bowel surgery within 24 weeks of baseline; history of gastrointestinal surgery within 8 weeks of baseline; and primary sclerosing cholangitis. Patients who had received TNF antagonists within 2 months or 5 times the respective elimination half-life (whichever was longer) before baseline or vedolizumab, rituximab, efalizumab, or natalizumab at any time were excluded.

Investigational Products and Treatment Procedure

Abrilumab was provided as a sterile, colorless to slightly yellow, frozen liquid at 70 mg/mL in glass vials containing an approximately 1-mL deliverable volume for single use only. Placebo was provided as a frozen liquid identical in appearance, storage, and packaging to abrilumab. Unblinded pharmacists used vialed placebo to dilute vialed abrilumab to prepare lower doses. Placebo and abrilumab were administered by SC injection. Irrespective of treatment arm, blinding was maintained by all patients receiving 3 separate SC injections for a total volume of 3 mL per dose. During the open-label period, patients received abrilumab 210 mg every 3 months by 3 SC injections for a total volume of 3 mL.

Assessments

The primary end point was remission at week 8 (total Mayo Score ≤2 points, with no individual sub-score >1 point). Key secondary end points were response at week 8 (decrease from baseline in total Mayo Score ≥3 points and ≥30% decrease from baseline, with an accompanying decrease in the sub-score for rectal bleeding ≥1 point or an absolute sub-score for rectal bleeding 0 or 1) and mucosal healing at week 8 (absolute endoscopic sub-score 0 or 1). Another secondary end point was sustained remission at weeks 8 and 24. For safety end points, data from all randomized patients who received ≥1 dose of double-blind treatment were assessed based on actual treatment received; there was no statistical testing for safety analyses. Safety was assessed by monitoring adverse events (AEs), serious AEs (SAEs), significant changes in laboratory values and vital signs, and anti-abrilumab antibodies. The neurologic status of patients was closely monitored throughout the study and for up to 24 months after the last dose of investigational product (IP) using a prespecified checklist. An external independent progressive multifocal leukoencephalopathy (PML) adjudication committee with expertise in neurologic manifestations of PML reviewed clinical data and applied a prespecified diagnostic algorithm for PML.

Immunogenicity Assessment

Serum anti–abrilumab-binding antibodies were assessed using validated electro-chemiluminescent immunoassays: screening assay, specificity assay, and quasi-quantitative titration assay. The immunoassay (binding) drug tolerance was 25 μg/mL. Anti–abrilumab-neutralizing antibodies were analyzed for samples positive for anti–abrilumab-binding antibodies using a cell-based (CHO-$\alpha_4\beta_7$ cell) assay. The drug tolerance of the neutralizing antibody assay was 0.063 μg/mL.

Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic. Characterization of abrilumab PK and the exposure–response relation for efficacy were exploratory end points. The bioanalytical assay to determine abrilumab serum concentration is described elsewhere.[15,16] Additional details about the PK assay and analyses are presented in the Supplementary Materials.

Fecal Calprotectin and Serum C-Reactive Protein. The effects of abrilumab on fecal calprotectin (FCP) and serum concentrations of C-reactive protein (CRP) were exploratory end points. Fecal samples were collected within 3 days before or during specified study visits for quantitative determination of FCP. Covance Central Laboratory Services (Princeton, NJ) performed the diagnostic (enzyme immunoassay) test.

Flow Cytometry. A sub-study of 129 patients (48, 7, 21, 37, and 29 patients in the placebo, abrilumab 7-mg, 21-mg, 70-mg, and 210-mg arms, respectively), selected by geographic location near the central laboratory, was analyzed for baseline and post-dose changes in peripheral blood $\alpha_4\beta_7$ receptor occupancy. Additional details about receptor occupancy and flow cytometry methods are presented in the Supplementary Materials.

Statistical Analysis

Sample size considerations assumed the week-8 remission rates would be 7.5%, 12%, 16.5%, 21%, and 21% in the placebo and abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively, based on historical data and a linear dose–response relation. A total number of 360 patients was estimated based on the overall linear trend test to reach 80% power at a 2-sided .10 significance level. With a randomization ratio of 2:1:2:2:2 intended to allocate fewer patients to a potentially non-efficacious dose, planned sample sizes were 80, 40, 80, 80, and 80 patients for the placebo and abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively, with 77% power to detect differences between each of the abrilumab 210-mg and 70-mg groups vs placebo using a .10 2-sided test, assuming a 5% dropout rate.

Early during trial conduct, routine PK analyses by the unblinded clinical pharmacology group reported a systematic inconsistency in expected exposures for the 7-mg and 21-mg dose cohorts (Supplementary Figure 2). The study was immediately paused for investigation, which showed a consistent discrepancy between the IP instruction manual (IPIM) description of vial positions and the actual vial positions in the IP package (Supplementary Figure 3). The vial in the lower-left

corner ("position A" in Supplementary Figure 3) of the package was—according to the IPIM—intended to contain active IP (abrilumab); however, it was placebo. Likewise, the vial in "position C" was intended to be placebo, and it was active IP. Therefore, all patients randomized to abrilumab 21 mg until this point received placebo and all patients randomized to abrilumab 7 mg received 70 mg systematically. This was the sole error and unrelated to the Interactive Web Response System. As a consequence, the study up to the pause was randomized to 3 arms—placebo, 70 mg, and 210 mg—with a randomization ratio of 4:3:2; after the pause, the study was randomized to 5 arms—placebo, 7 mg, 21 mg, 70 mg, and 210 mg—with a randomization ratio of 2:1:2:2:2. Because the study remained blinded to randomized treatment assignment, trial integrity was maintained. The issue was termed a "misalignment of active (ie, abrilumab) vial positions in the package vs the IPIM" (also referred to as "misalignment").

Study sites, independent ethics committees or institutional review boards, and regulatory authorities were notified of this systematic error. Once the discrepancy was corrected and affected patients completed their double-blind treatment period, the study resumed enrollment and randomization per protocol. The protocol statistical analysis section was amended to account for the misalignment before study pause and updated to prespecify the appropriate analysis method before study unblinding. The sponsor study team, patients, and study sites remained blinded throughout this process. The misalignment resulted in a final randomization allocation of 116, 21, 40, 98, and 79 patients in the placebo and abrilumab 7-mg, 21-mg, 70-mg and 210-mg arms, respectively (Supplementary Figure 2).

The study was powered for formal statistical testing of the abrilumab 70-mg and 210-mg groups. To account for multiplicity of statistical testing, primary and key secondary end points for the 2 highest doses of abrilumab (70 and 210 mg) were tested at the end of the 8-week induction period under a sequential framework at a 2-sided significance level of .10 using the Bonferroni-based chain procedure.[17] Key secondary end points of response and mucosal healing were initially tested using .05 simultaneously until the hypothesis of the other chain was rejected, so end points could be re-tested at the .10 significance level. A single logistic regression model containing all abrilumab dose groups, placebo, baseline total Mayo Score, and stratification factors (prior vs no prior TNF antagonist use and enrollment pre- vs post-protocol amendment) was fit. The stratification factor of prior vs no prior TNF antagonist use was used in randomization. Odds ratios (ORs), 90% confidence intervals (CIs), and *P* values were obtained for pairwise comparisons of each abrilumab dose with placebo using this model, with nonresponder imputation (NRI). Non-adjusted (observed NRI) and adjusted (by logistic regression model) estimates of remission rates were calculated. Considering the sample size and the final randomization allocation, for the primary end point there was approximately 87% and 84% power to detect differences between the abrilumab 70-mg and 210-mg groups, respectively, vs placebo using a .10 2-sided test. The relation of the percentage of patients in remission was plotted against observed deciles of abrilumab serum trough concentration as part of the exposure–response analysis of data. Remission rates for different decile groups were tested for significance against the placebo remission rate.

Postulated response and mucosal healing rates based on sequential testing were 25%, 45%, and 45% in the placebo, abrilumab 70-mg, and abrilumab 210-mg groups, respectively. For the abrilumab 70-mg group and the 210-mg group vs placebo, the power to detect differences was approximately 85% for response and 81% for mucosal healing using a .05 2-sided test. The association between baseline $\alpha_4\beta_7$ level and change in total Mayo Score was analyzed based on baseline-adjusted analysis of variance for the change from baseline Mayo Score; the analysis included factors for baseline $\alpha_4\beta_7$, dose, and interaction.

Results

Patient Disposition

Of 359 patients randomized, 354 entered the double-blind phase; 116 patients (33%) received placebo and 238 (67%) received abrilumab. A systematic misalignment between IP secondary packaging and the IPIM led to a final allocation of placebo (n = 116), 7 mg (n = 21), 21 mg (n = 40), 70 mg (n = 98), and 210 mg (n = 79). Importantly, the misalignment did not compromise the study blind and data were analyzed per the protocol amendment described in the Methods.

At week 8, 332 patients (94%) completed the initial 8-week double-blind period (abrilumab, 226 [95%]; placebo, 106 [91%]); 6 patients (3 abrilumab, 3 placebo) completed but missed the week-8 assessment (Supplementary Figure 4). Overall, the most common reasons for discontinuation before week 8 were full withdrawal of consent (abrilumab, 5 [2.1%]; placebo, 1 [0.9%]), AEs (abrilumab, 1 [0.4%]; placebo, 4 [3.4%]), and requirement for alternative therapy (abrilumab, 3 [1.3%]; placebo, 2 [1.7%]). Of 354 patients who received double-blind treatment, 153 (43%) completed the 24-week double-blind period (abrilumab, 118 [50%]; placebo, 35 [30%]). The most common reason for discontinuation of the double-blind period before week 24 was lack of response (abrilumab, 78 [33%]; placebo, 54 [47%]). Of 354 patients who received double-blind treatment, 311 (88%) entered the open-label period.

Patient Characteristics

Baseline demographics and disease characteristics were similar among treatment groups, with no notable differences among the abrilumab 70-mg, abrilumab 210-mg, and placebo groups (Table 1). Overall, mean age was 40.1 years (standard deviation [SD] 12.4). Mean baseline total Mayo Score based on central blinded reading of sigmoidoscopies was 8.9 (SD 1.5) and mean duration of disease was 8.6 years (SD 6.7). Approximately 51% of patients had prior exposure to $\geq$1 TNF antagonist and 44% used oral corticosteroids at baseline. Median overall baseline FCP was 579 mg/kg, and median baseline CRP was 4.8 mg/L.

Efficacy

Primary End Point. Non-adjusted remission rates (total Mayo Score $\leq$2 points with no individual sub-score $>$1 point) at week 8 were 4.3% for placebo and 0.0%,

Table 1. Demographic and Disease Characteristics at Baseline

Characteristic	Placebo (n = 116)	Abrilumab 7 mg Q4W (n = 21)	Abrilumab 21 mg Q4W (n = 40)	Abrilumab 70 mg Q4W (n = 98)	Abrilumab 210 mg (n = 79)	Abrilumab All (N = 238)	Total (N = 354)
Men, n (%)	80 (69.0)	14 (66.7)	28 (70.0)	67 (68.4)	48 (60.8)	157 (66.0)	237 (66.9)
Caucasian, n (%)	108 (93.1)	19 (90.5)	39 (97.5)	87 (88.8)	77 (97.5)	222 (93.3)	330 (93.2)
Age (*y*), median (IQR)	40.0 (29.5–50.5)	48.0 (31.0–54.0)	36.5 (29.0–47.0)	39.0 (30.0–48.0)	39.0 (31.0–50.0)	39.0 (31.0–49.0)	39.0 (30.0–50.0)
BMI (kg/m^2), mean (SD)	25.1 (4.6)	24.8 (4.7)	25.0 (4.4)	26.0 (5.8)	25.3 (4.2)	25.5 (5.0)	25.3 (4.8)
Duration of UC (*y*), median (IQR)	6.4 (3.2–11.2)	7.4 (4.3–11.3)	5.7 (3.4–10.0)	7.4 (3.4–13.6)	8.4 (3.5–12.5)	7.2 (3.5–12.3)	7.1 (3.4–11.8)
Total Mayo Score,[a] median (IQR)	9.0 (8.0–10.0)	8.0 (7.0–9.0)	8.5 (7.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Partial Mayo Score, mean (SD)	6.3 (1.4)	5.6 (1.3)	6.0 (1.4)	6.3 (1.3)	6.4 (1.2)	6.2 (1.3)	6.2 (1.3)
Albumin (*g/L*), mean (SD)	37.6 (4.7)	38.9 (4.7)	39.2 (6.1)	38.7 (4.6)	38.8 (4.1)	38.8 (4.7)	38.4 (4.7)
FCP (*mg/kg*), median (IQR)	584.0 (193.3–1444.2)	568.4 (171.7–895.5)	611.8 (465.2–1161.6)	522.8 (162.5–963.3)	587.6 (340.7–1209.1)	574.5 (235.6–1112.3)	578.5 (211.4–1185.0)
CRP (*mg/L*), median (IQR)	6.4 (2.0–14.0)	5.0 (2.2–15.4)	2.2 (1.0–7.9)	5.0 (1.4–10.3)	4.1 (1.6–11.8)	4.3 (1.4–11.0)	4.8 (1.5–12.7)
Prior TNF antagonist, n (%)	72 (62.1)	5 (23.8)	10 (25.0)	55 (56.1)	38 (48.1)	108 (45.4)	180 (50.8)
Prior immunomodulator use, n (%)	106 (91.4)	17 (81.0)	33 (82.5)	89 (90.8)	59 (74.7)	198 (83.2)	304 (85.9)
Immunomodulator use at baseline, n (%)	48 (41.4)	6 (28.6)	17 (42.5)	32 (32.7)	21 (26.6)	76 (31.9)	124 (35.0)
Oral corticosteroid use at baseline, n (%)	53 (45.7)	6 (28.6)	16 (40.0)	49 (50.0)	32 (40.5)	103 (43.3)	156 (44.1)
5-aminosalicylate use at baseline, n (%)	73 (62.9)	13 (61.9)	29 (72.5)	70 (71.4)	60 (75.9)	172 (72.3)	245 (69.2)

BMI, body mass index; IQR, interquartile range; Q4W, every 4 weeks.
[a]Based on central read of flexible recto-sigmoidoscopy.

2.5%, 13.3%, and 12.7% for the abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively (Figure 1). The odds of achieving remission at week 8 were significantly greater with the abrilumab 70-mg and 210-mg doses vs placebo (70 mg: OR 3.35; 90% CI 1.41–7.95; $P = .021$; 210 mg: OR 3.33; 90% CI 1.34–8.26; $P = .030$; Table 2).

Key Secondary End Points. Non-adjusted response rates at week 8 were 25.9% for placebo and 14.3%, 50.0%, 49.0%, and 46.8% for the abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively (Figure 2). The odds of achieving response at week 8 were significantly greater with the abrilumab 70-mg and 210-mg doses vs placebo (70 mg: OR 2.78; 90% CI 1.71–4.52; $P < .001$; 210 mg: OR 2.57; 90% CI 1.53–4.51; $P = .003$; Supplementary Table 1). Non-adjusted mucosal healing rates at week 8 were 21.6% for placebo and 14.3%, 15.0%, 32.7%, and 29.1% for the abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively (Figure 3). The odds of achieving mucosal healing rates at week 8 were significantly greater with the abrilumab 70-mg and 210-mg doses vs placebo (70 mg: OR 2.34; 90% CI 1.35–4.07; $P = .011$; 210 mg: OR 2.10; 90% CI 1.15–3.82; $P = .041$; Supplementary Table 2).

Other Secondary and Exploratory Clinical End Points. Subgroup analyses were conducted for primary and key secondary end points in patients with prior TNF antagonist treatment failure vs no prior TNF antagonist use. Analysis of patients by prior TNF antagonist failure indicated greater remission rates for patients treated with the abrilumab 70-mg and 210-mg doses vs placebo (70 mg: OR 5.14; 90% CI 1.11–23.81; $P = .079$; 210 mg: OR 11.06; 90% CI 2.39–51.13; $P = .010$; Figure 1). Greater response (OR 2.91; 90% CI 1.45–5.84; $P = .012$; Figure 2) and mucosal healing rates (OR 3.59; 90% CI 1.60–8.08; $P = .009$; Figure 3) were observed for patients with prior TNF antagonist failure treated with abrilumab 210 mg vs placebo. Nominal P values for remission were not significant in patients with no prior TNF antagonist use (Table 2); however, nominal P values were significant for response in the 21- and 70-mg groups and mucosal healing in the 70-mg group (Supplementary Tables 1 and 2).

There was no indication of treatment effect of abrilumab for remission and response at week 24 (Supplementary Tables 3 and 4). For mucosal healing at week 24, there was an indication of treatment effect for the abrilumab 70-mg group (Supplementary Table 5). Of 354 randomized patients who received ≥1 dose of IP, 140 (40%) had total Mayo Scores at weeks 8 and 24 and were evaluable for sustained remission. Among evaluable patients, 8 of 46 (17.4%) on abrilumab 70 mg, 3 of 32 (9.4%) on abrilumab 210 mg, and 3 of 32 (9.4%) on placebo had remission at weeks 8 and 24 (Supplementary Table 6). Using NRI for patients not evaluable for sustained remission, the adjusted sustained remission rate difference for abrilumab 70 mg vs placebo was 5.8% (90% CI −0.6 to 10.4), with OR 2.94 (90% CI 1.03–8.36); the adjusted sustained remission rate difference for abrilumab 210 mg vs placebo was 1.0% (90% CI −4.7 to 4.6), with OR 1.32 (90% CI 0.38–4.56). Of patients who achieved response at week 8, 12 of 30 (40.0%), 21 of 48 (43.8%), and 8 of 37 (21.6%) achieved remission at week 24 in the placebo, abrilumab 70-mg, and abrilumab 210-mg groups, respectively, using NRI. Steroid-free remission at week 24 was 5 of 116 (4.3%), 7 of 98 (7.1%), and 4 of 79 (5.1%) patients in the placebo, abrilumab 70-mg, and abrilumab 210-mg groups, respectively, using NRI (Supplementary Table 7).

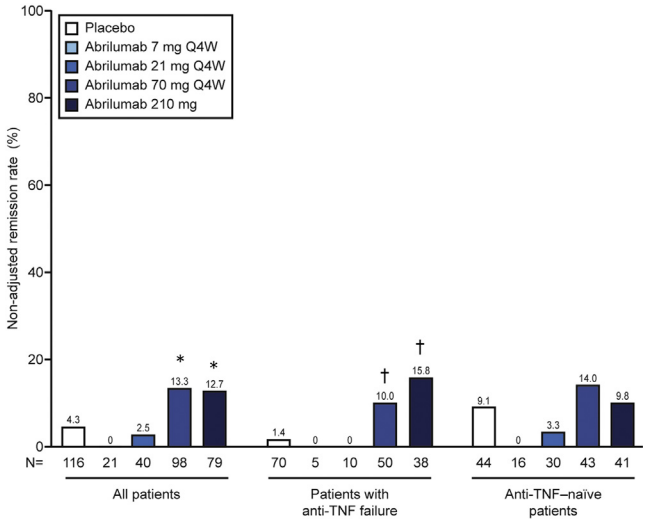


Figure 1. Non-adjusted remission rates for all patients, patients with prior TNF antagonist failure, and patients naïve to TNF antagonist at week 8. Patients received SC placebo or abrilumab 7 mg, 21 mg, or 70 mg (on day 1, week 2, week 4, and Q4W thereafter) or a single dose of abrilumab 210 mg (on day 1 followed by placebo weeks 2 and 4 and Q4W thereafter). Remission at week 8 was indicated by a total Mayo Score ≤2 points, with no individual sub-score >1 point. Non-adjusted remission rates, 90% CIs, and P values were obtained from a logistic regression model for pairwise comparisons of abrilumab dose groups vs placebo group with adjustment for stratification factors (prior vs no prior TNF antagonist use) and for baseline total Mayo Score using NRI; bars represent 90% CIs around means. Nominal P values are reported for exploratory end points without adjustment for multiple testing. *Significant at $P < .1$; †nominal $P < .1$. N, number of patients in full analysis set; Q4W, every 4 weeks.

Safety

Adverse Events. Patients reported AEs at similar incidences across treatment groups through week 24: 79 (68.1%) patients in the placebo and 150 (63.0%) patients in all abrilumab groups reported ≥1 treatment-emergent AE of any grade (Table 3). Mild injection site reactions were reported by 4 (3.4%) patients in the placebo group, 5 (5.1%) in abrilumab 70-mg group, and 1 (1.3%) in abrilumab 210-mg group. Grade ≥3 AEs were reported by 16 (13.8%) patients in the placebo group and 24 (10.1%) across all abrilumab groups. AEs led to discontinuation in 10 (8.6%) patients in the placebo group and 8 (3.4%) in the abrilumab groups. SAEs were reported by 14 (12%) and 16 (6.7%) patients in the placebo and abrilumab groups, respectively. Grade ≥3 SAEs were reported by 9.5% and 5.5% of patients in the placebo and abrilumab groups, respectively. The only SAE reported by more than 1 patient treated with abrilumab

Table 2. Summary of Remission at Week 8

		Abrilumab			
	Placebo	7 mg Q4W	21 mg Q4W	70 mg Q4W	210 mg
All patients, N	116	21	40	98	79
Non-adjusted remission rate using NRI, n (%)	5 (4.3)	0	1 (2.5)	13 (13.3)	10 (12.7)
Adjusted remission rate using NRI, %	4.4	1.6	2.9	13.5	13.4
Difference, % (90% CI)	—	−2.9 (−5.5 to 5.4)	−1.6 (−5.2 to 5.5)	9.0 (1.6–14.6)	8.9 (0.8–14.9)
OR (90% CI)		0.34 (0.03–4.33)	0.64 (0.13–3.17)	3.35 (1.41–7.95)	3.33 (1.34–8.26)
P value		.49	.64	.021	.030
Patients with TNF antagonist failure, n	70	5	10	50	38
Non-adjusted remission rate using NRI, n (%)	1 (1.4)	0	0 (0)	5 (10)	6 (15.8)
Adjusted remission rate using NRI, %	1.4	11.2	5.5	7.0	13.9
Difference, % (90% CI)	—	9.8 (−24.3 to 22.4)	4.0 (−13.7 to 10.4)	5.5 (−2.5 to 10.2)	12.4 (0.9–19.9)
OR (90% CI)		8.68 (0.32–233.49)	3.98 (0.17–94.14)	5.14 (1.11–23.81)	11.06 (2.39–51.13)
P value		.28	.47	.079	.010
Patients naïve to TNF antagonist, n	44	16	30	43	41
Non-adjusted remission rate using NRI, n (%)	4 (9.1)	0	1 (3.3)	6 (14.0)	4 (9.8)
Adjusted remission rate using NRI, %	7.3	1.3	2.7	14.0	8.8
Difference, % (90% CI)	—	−6.0 (−9.7 to 6.3)	−4.6 (−9.9 to 6.3)	6.7 (−6.4 to 15.3)	1.5 (−10.6 to 8.9)
OR (90% CI)		0.17 (0.01–2.30)	0.36 (0.07–1.85)	2.07 (0.68–6.32)	1.22 (0.38–3.98)
P value		.27	.30	.29	.78

NOTE. Remission at week 8 was defined as a total Mayo Score ≤2 points, with no individual sub-score >1 point.
N, number of patients in full analysis set; n, number of patients who reached remission status at week 8; Q4W, every 4 weeks.

was worsening of UC. No patient died or reported PML during the study. Ten (8.6%) patients in the placebo group and 9 (3.8%) in the abrilumab groups reported benign, malignant, and unspecified neoplasms (Table 3).

Immunogenicity. Post-baseline anti-abrilumab antibody evaluation from 348 patients (placebo, 114; abrilumab, 234) indicated 1 patient in the abrilumab 70-mg group and 1 in the abrilumab 210-mg group were positive for anti–abrilumab-binding antibodies. No neutralizing antibodies were detected.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics. Of 63 patients who participated in the PK sub-study, 23 had enough data for PK parameter evaluation: 3 patients in the abrilumab 7-mg group, 6 in the 21-mg group, 5 in the 70-mg group, and 9 in the 210-mg group. Based on the abrilumab PK profile and parameters analysis, the mean values for maximum observed concentration were 2.48 μg/mL (SD 3.06), 6.43 μg/mL (2.80), 18.3 μg/mL (9.08), and 27.5 μg/mL (10.4) for the abrilumab 7-mg, 21-mg, 70-mg, and 210-mg arms, respectively. The median times to maximum observed concentration were 8.0, 6.5, 7.0, and 7.9 days for abrilumab 7 mg, 21 mg, 70 mg, and 210 mg, respectively (Supplementary Table 8). After SC administration of abrilumab 210 mg every 3 months in the open-label period, with the number of patients varying greatly (14–241 patients) depending on time point, mean trough concentrations ranged from 3.55 to 5.65 μg/mL. Mean (SD) PK concentrations at weeks 8 and 24 are presented in Supplementary Table 9.

Exposure–Response Analysis. Exposure–response analysis of remission rate and PK data demonstrated that patients in decile groups with mean trough levels of ≥10 μg/mL showed significant remission vs placebo, and maximal observed remission rates were associated with mean trough concentrations >10 μg/mL (Supplementary Figure 5).

Change in CRP and FCP. CRP and FCP concentrations for weeks 8 and 24 are presented in Supplementary Tables 10 and 11, respectively. Up to week 8, treatment-related decreases were observed for the abrilumab 70-mg and 210-mg groups vs placebo for FCP, but not for CRP. At week 8, post hoc analyses showed only patients in the abrilumab 70-mg arm attained a 50% decrease of FCP from baseline (adjusted rate) vs placebo; treatment difference was 17% (90% CI 3.6–27.9) for the abrilumab 70-mg group vs placebo (Supplementary Table 11). The nominal *P* value for the corresponding OR vs placebo was .03. In contrast, the CRP treatment difference vs placebo at week 8 appeared to be minimal for all abrilumab doses.

Sub-study of Immunophenotyping Receptor Occupancy With Absolute Counts. *Assessment of Free* $\alpha_4\beta_7$. Abrilumab treatment led to a reversible decrease of free $\alpha_4\beta_7$ levels on naïve $CD4^+$ T cells in the peripheral blood of patients with UC (Supplementary Figure 6*A*). Maximal decrease in free $\alpha_4\beta_7$ levels was approximately 90% from baseline. Maximal decrease in free $\alpha_4\beta_7$ levels compared with baseline was observed at the first post-dose assessment (week 2) for all dosages of abrilumab. For patients in the abrilumab 7-mg multidose arm, the decrease persisted through week 4. From weeks 8 through 24, mean free $\alpha_4\beta_7$ levels began to normalize but remained 65% decreased compared with baseline and were not statistically different from means at weeks 2 and 4. For patients in the 21-mg and 70-mg multiple-dose arms, maximal decrease in free $\alpha_4\beta_7$ levels persisted at nearly those low levels through week 24. For patients in the 210-mg single-dose arm,

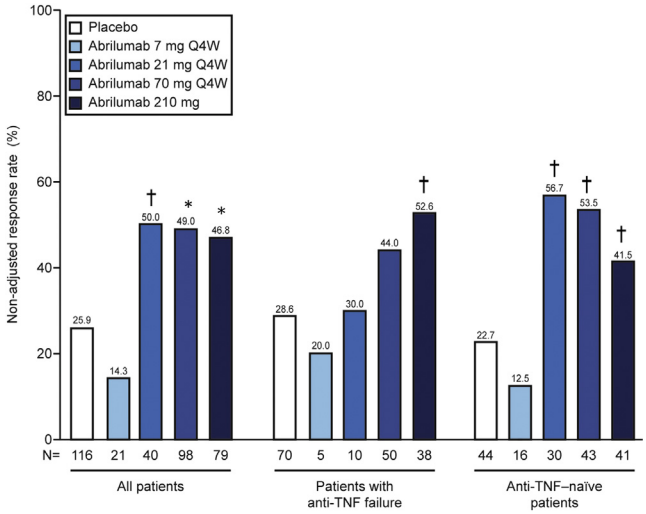


Figure 2. Non-adjusted response rates for all patients, patients with prior TNF antagonist failure, and patients naïve to TNF antagonist at week 8. Patients received SC placebo or abrilumab at 7 mg, 21 mg, or 70 mg (on day 1, week 2, week 4, and Q4W thereafter) or a single dose of abrilumab 210 mg (on day 1 followed by placebo weeks 2 and 4 and Q4W thereafter). Response at week 8 was indicated by a decrease from baseline in total Mayo Score ≥3 points and ≥30% decrease from baseline, with an accompanying decrease in the sub-score for rectal bleeding of ≥1 point or an absolute sub-score for rectal bleeding 0 or 1. Non-adjusted response rates, 90% CIs, and *P* values were obtained from a logistic regression model for pairwise comparisons of the abrilumab dose groups vs placebo group with adjustment for stratification factors (prior vs no prior TNF antagonist use) and for baseline total Mayo Score using NRI; bars represent 90% CIs around means. Nominal *P* values are reported for exploratory end points without adjustment for multiple testing. *Significant at $P < .1$; †nominal $P < .1$. N, number of patients in full analysis set; Q4W, every 4 weeks.

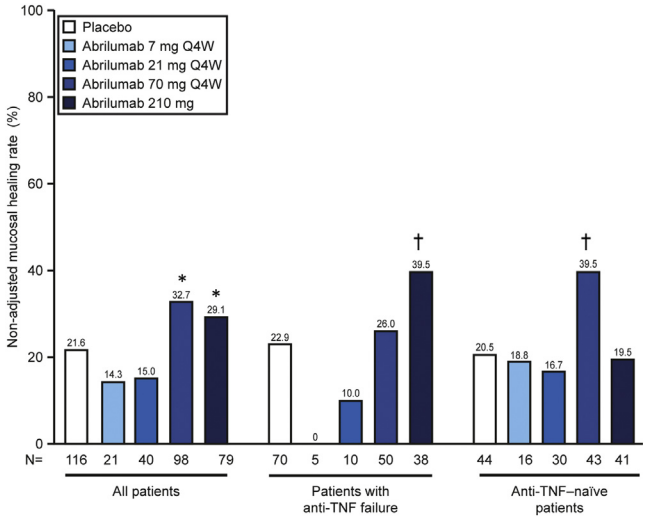


Figure 3. Non-adjusted mucosal healing rates for all patients, patients with prior TNF antagonist failure, and patients naïve to TNF antagonist at week 8. Patients received SC placebo or abrilumab at 7 mg, 21 mg, 70 mg (on day 1, week 2, week 4, and Q4W thereafter) or a single dose of abrilumab 210 mg (on day 1 followed by placebo weeks 2 and 4 and Q4W thereafter). Mucosal healing at week 8 was indicated by a absolute sub-score for recto-sigmoidoscopy 0 or 1. Non-adjusted mucosal healing rates, 90% CIs, and *P* values were obtained from a logistic regression model for pairwise comparisons of the abrilumab dose groups vs placebo group with adjustment for stratification factors (prior vs no prior TNF antagonist use) and for baseline total Mayo Score using NRI; bars represent 90% CIs around means. Nominal *P* values are reported for exploratory end points without adjustment for multiple testing. *Significant at $P < .1$; †nominal $P < .1$. N, number of patients in full analysis set; Q4W, every 4 weeks.

maximal decrease in free $\alpha_4\beta_7$ levels persisted through week 8. Intermediate levels of free $\alpha_4\beta_7$ were observed at weeks 12 and 16, and free $\alpha_4\beta_7$ levels returned to baseline at week 24.

Assessment of Total $\alpha_4\beta_7$. Abrilumab led to a reversible decrease in total $\alpha_4\beta_7$ levels in the peripheral blood of patients with UC. Maximal decrease was approximately 50% of baseline. Duration of decrease in total $\alpha_4\beta_7$ levels roughly mirrored the change in free $\alpha_4\beta_7$, including an intermediate decrease—from 0% to 50%—in total $\alpha_4\beta_7$ levels in the 7-mg group at weeks 12 and 24 (no patients in the 7-mg group had a week-16 visit). The 210-mg group likewise exhibited an intermediate decrease in total $\alpha_4\beta_7$ levels at weeks 12 and 16, with a return to baseline of total $\alpha_4\beta_7$ at week 24 (Supplementary Figure 6*B*). Baseline total $\alpha_4\beta_7$ levels were significantly lower in patients who had prior TNF antagonist failure (Supplementary Figure 7).

Prognostic Biomarker. Mean free and total $\alpha_4\beta_7$ levels on naïve $CD4^+$ T cells at baseline were significantly lower in patients with UC than in healthy volunteers from previous abrilumab studies and validation studies (data on file, Amgen Inc; $P = .001$ and $P = .0045$, respectively). Although the decrease in the number of $\alpha_4\beta_7^+$ circulating memory T cells has been observed previously,[18] decrease of $\alpha_4\beta_7$ levels on naïve $CD4^+$ T cells in UC was unexpected. Therefore, we tested whether baseline levels of $\alpha_4\beta_7$ on naïve $CD4^+$ T cells could identify patients most likely to respond to abrilumab. Overall, there was a significant linear association between higher baseline $\alpha_4\beta_7$ levels and greater changes in total Mayo Score ($P = .046$; Supplementary Figure 8) and in mucosal healing ($P = .03$; data not shown) at week 8. However, this association was not significantly different among any dose groups ($P = .53$), with higher baseline levels predicting a greater change in total Mayo Score and mucosal healing at week 8 in the placebo group.

Assessment of CD4 T-Cell Subsets. Administration of abrilumab induced a significant post-dose increase in mean $\alpha_4\beta_7$–high central memory $CD4^+$ T-cell counts ($P = .016$ by analysis of variance) but not in mean circulating or central memory $CD4^+$ T-cell counts from baseline to week 8 (Supplementary Figure 6*C*).

Discussion

This randomized phase 2b study demonstrated that treatment with the anti-$\alpha_4\beta_7$ antibody abrilumab, administered as multiple doses of 70 mg or a single dose of 210 mg, significantly improved 8-week remission rates compared with placebo for patients with moderate-to-severe UC

Table 3. Treatment-Emergent Adverse Events Reported by ≥5% of Patients in Any Treatment Arm in the Safety Population

Adverse event, n (%)	Placebo n = 116)	Abrilumab 7 mg Q4W (n = 20)	Abrilumab 21 mg Q4W (n = 40)	Abrilumab 70 mg Q4W (n = 99)	Abrilumab 210 mg (n = 79)	Abrilumab All (N = 238)
Any	79 (68.1)	9 (45.0)	21 (52.5)	70 (70.7)	50 (63.3)	150 (63.0)
Nasopharyngitis	7 (6.0)	0	6 (15.0)	9 (9.1)	8 (10.1)	23 (9.7)
Ulcerative colitis	9 (7.8)	0	3 (7.5)	11 (11.1)	8 (10.1)	22 (9.2)
Headache	7 (6.0)	1 (5.0)	2 (5.0)	11 (11.1)	8 (10.1)	22 (9.2)
Arthralgia	6 (5.2)	0	4 (10.0)	11 (11.1)	6 (7.6)	21 (8.8)
Fatigue	3 (2.6)	0	1 (2.5)	8 (8.1)	3 (3.8)	12 (5.0)
Diarrhea	1 (0.9)	0	3 (7.5)	3 (3.0)	5 (6.3)	11 (4.6)
Nausea	4 (3.4)	0	2 (5.0)	4 (4.0)	5 (6.3)	11 (4.6)
Neoplasm[a]	10 (8.6)	2 (9.5)	1 (2.5)	2 (2.0)	4 (5.1)	9 (3.8)
Anemia	2 (1.7)	0	3 (7.5)	2 (2.0)	2 (2.5)	7 (2.9)
Cough	2 (1.7)	0	0	5 (5.1)	2 (2.5)	7 (2.9)
Abdominal pain	5 (4.3)	1 (5.0)	3 (7.5)	1 (1.0)	1 (1.3)	6 (2.5)
Injection site reaction	4 (3.4)	0	0	5 (5.1)	1 (1.3)	6 (2.5)
Hypertension	1 (0.9)	0	0	5 (5.1)	0	5 (2.1)
Influenza	4 (3.4)	2 (10.0)	0	2 (2.0)	0	4 (1.7)
Candida infection	0	2 (10.0)	0	0	0	2 (0.8)
Serious adverse event	14 (12.1)	1 (5.0)	3 (7.5)	5 (5.1)	7 (8.9)	16 (6.7)

NOTE. Adverse events were classified according to the Medical Dictionary for Regulatory Activities System (Version 18.1) by preferred terms.
Q4W, every 4 weeks.
[a]Benign, malignant, and unspecified (including cysts and polyps): acrochordon (n = 1, placebo; n = 1, 210 mg); adenoma benign (n = 1, 210 mg); angiolipoma (n = 1, 7 mg Q4W); bladder cancer (n = 1, placebo); bone giant cell tumor benign (n = 1, 210 mg); colon adenoma (n = 1, placebo; n = 1, 7 mg Q4W); hemangioma (n = 1, placebo); leiomyoma (n = 1, placebo); lipoma (n = 1, 210 mg); prostatic adenoma (n = 1, 210 mg); skin cancer (n = 1, placebo); skin papilloma (n = 2, placebo; n = 2, 70 mg Q4W); thyroid neoplasm (n = 1, 21 mg Q4W); and uterine leiomyoma (n = 2, placebo).

whose previous conventional therapies had failed. Significant improvements also were observed for the 2 dosages of abrilumab compared with placebo for key secondary efficacy end points of clinical response and mucosal healing at week 8.

There was no apparent advantage of multiple doses of 70 mg or a single dose of 210 mg of abrilumab, with the 2 dosages resulting in adjusted remission rates of approximately 13.5%, lower than the 21% anticipated in the sample size calculation. However, these estimates were 3-fold greater than that observed with placebo; remission was achieved for only 4.4% of patients who received placebo, indicating a refractory UC population. Clinical response was achieved by almost half the patients and mucosal healing was achieved by almost one third of patients treated with abrilumab 70 or 210 mg compared with 26% and 16.8% who received placebo, respectively. Improvements in these outcome measures were less clear at week 24. Notably, treatment effect with the 2 higher dosages of abrilumab at week 8 was apparent across all prespecified end points for patients with prior TNF antagonist failure, suggesting $\alpha_4\beta_7$ inhibition with abrilumab might be a viable treatment alternative for patients who have lost the response to or cannot tolerate TNF antagonists. However, in the TNF-naïve subpopulation, nominal *P* values for remission rates were not significant as in the overall study population, although nominal *P* values for response and mucosal healing rates were significant in the 21- and 70-mg groups, respectively. However, caution should be observed when interpreting these subgroup analyses, because the statistical power required for precise estimates of relative efficacy was insufficient because of the smaller sample.

Other monoclonal antibodies targeting the $\alpha_4\beta_7$–mucosal addressin cell adhesion molecule-1 interaction, including vedolizumab (anti-$\alpha_4\beta_7$) and etrolizumab (anti-β_7), are under investigation in clinical trials for UC, with vedolizumab already approved for treatment of patients with UC and Crohn's disease.[19] Induction of response observed in the present trial of abrilumab appeared similar to that observed in a phase 3 trial using an induction dosage of vedolizumab 300 mg at weeks 0 and 2 (47.1% vs 25.5% in placebo group at week 6).[20] Increases in clinical remission and mucosal healing rates observed with abrilumab also were similar to those with vedolizumab at week 6.[20] The phase 3 GEMINI I trial of vedolizumab included a maintenance phase, during which durability of response was measured in responders to induction therapy who were re-randomized to continued administration of vedolizumab vs placebo (drug withdrawal trial design) for up to 52 weeks.[21] In the present, smaller study of abrilumab, patients continued their original treatment assignment to week 24 irrespective of response at week 8 ("treat straight through" trial design, which does not select for responding patients), and sustained remission to week 24 was assessed as a secondary end point. Although the odds of sustained remission increased for patients who continued to take multiple doses of abrilumab 70 mg every

4 weeks compared with placebo, interpretation was limited by the small number of patients who provided data at weeks 8 and 24 and could have been affected by inadequate exposure of drug later in the study. In a phase 2 trial of patients with moderate-to-severe UC, treatment with etrolizumab 100 mg led to achievement of clinical remission in 21% of patients vs none with placebo at week 10, which is higher than that observed in our study at week 8.[22] However, clinical remission with etrolizumab was mainly reported in patients who were naïve to TNF antagonists, a less treatment-refractory population.

Based on the exposure–response analysis of the percentage of patients in remission and serum abrilumab trough concentrations, remission rates associated with abrilumab trough concentrations of $\geq$10 μg/mL are significantly different than placebo, suggesting maximal observed remission rates are achieved with abrilumab trough concentrations of $\geq$10 μg/mL. This abrilumab trough serum concentration is higher than exposure levels associated with 90% occupancy of $\alpha_4\beta_7$ (90% effective concentration 0.09 μg/mL) from the single ascending dose study of abrilumab in healthy volunteers.[15]

We observed significant associations between baseline $\alpha_4\beta_7$ levels and change in Mayo Score and mucosal healing, irrespective of treatment received during the study. Our results show that higher baseline concentrations of $\alpha_4\beta_7$ levels were a favorable prognostic indicator in UC disease activity and Mayo Score response, but not a predictive biomarker of abrilumab response. The association between baseline $\alpha_4\beta_7$ and overall outcome changes the probability of response (based on a threshold change in Mayo Score) by approximately $\geq$10% (depending on the dose) for a doubling in $\alpha_4\beta_7$ levels. In contrast to the expectation that baseline $\alpha_4\beta_7$ levels would be higher in patients who had used a TNF antagonist, we found baseline $\alpha_4\beta_7$ levels were significantly lower in patients with prior TNF antagonist failure. Prior exposure to TNF antagonist treatment was not found to affect abrilumab mean trough concentrations. The results of our exposure–response analyses suggest that greater abrilumab exposure might result in higher remission and response rates; there did not appear to be a correlation between remission and response rates and peripheral receptor occupancy.

Treatment with abrilumab for 8 weeks was well tolerated, with 95% of abrilumab-treated patients completing the week-8 assessment and only 1 patient discontinuing from the induction period for an AE. The most common AEs reported with abrilumab were anticipated: non-serious infections, gastrointestinal AEs, headache, and arthralgia. No PML cases were reported. Overall, the safety and tolerability of abrilumab do not appear to differ from those of vedolizumab and etrolizumab. Anti–abrilumab-binding antibodies were identified in 2 patients during the study, 1 each in the 70-mg and 210-mg groups; no neutralizing antibodies were detected.

This study has some limitations. A systematic misalignment of treatments led some patients randomized to the abrilumab 7-mg group to erroneously receive 70 mg and some randomized to the abrilumab 21-mg group to erroneously receive placebo. However, a protocol amendment permitting data from these patients to be analyzed based on actual treatment received, without breaking the study blind, allowed maintenance of trial integrity with minimal change in power to detect treatment differences between the 2 high-dose abrilumab groups and placebo. In addition, this short-term study did not fully evaluate continued treatment with abrilumab after induction of remission at 8 weeks. Although we observed a trend toward treatment effect at week 24 for the abrilumab 70-mg multidose group, longer-term, phase 3 studies evaluating clinical remission and response rates beyond 24 weeks are required to draw conclusions on the durability of treatment response. Conclusions regarding treatment responses based on prior TNF antagonist treatment are limited, but initial findings suggest potential benefit in TNF antagonist-naïve and -experienced patients.

Conclusion

The results from this phase 2 study provide preliminary evidence that abrilumab administered as multiple doses of 70 mg or a single dose of 210 mg might induce remission, clinical response, and mucosal healing in patients with moderate-to-severe UC. Overall, abrilumab has an acceptable safety and tolerability profile at the SC dosages administered in this patient population. Our data further support the mechanism of targeting the $\alpha_4\beta_7$ pathway as a therapeutic option for the management of moderate-to-severe UC and the use of $\alpha_4\beta_7$ levels as a potential prognostic indicator in UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.11.035.

References

1. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ 2013;346:f432.
2. Park SC, Jeen YT. Current and emerging biologics for ulcerative colitis. Gut Liver 2015;9:18–27.
3. Ordas I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012;380:1606–1619.
4. Affronti A, Orlando A, Cottone M. An update on medical management on Crohn's disease. Expert Opin Pharmacother 2015;16:63–78.
5. Devlin SM, Panaccione R. Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up. Med Clin North Am 2010;94:1–18.
6. Kornbluth A, Sachar DB. Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501–523; quiz 524.
7. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of

nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology 2015;148:1035–1058 e3.
8. Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell 2002;110:673–687.
9. Pals ST, de Gorter DJ, Spaargaren M. Lymphoma dissemination: the other face of lymphocyte homing. Blood 2007;110:3102–3111.
10. Schweighoffer T, Tanaka Y, Tidswell M, et al. Selective expression of integrin alpha 4 beta 7 on a subset of human CD4+ memory T cells with hallmarks of gut-trophism. J Immunol 1993;151:717–729.
11. Erle DJ, Briskin MJ, Butcher EC, et al. Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. J Immunol 1994;153:517–528.
12. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711–721.
13. Pan WJ, Hsu H, Rees WA, et al. Pharmacology of AMG 181, a human anti-alpha4 beta7 antibody that specifically alters trafficking of gut-homing T cells. Br J Pharmacol 2013;169:51–68.
14. Pan WJ, Radford-Smith G, Andrews JM, et al. Pharmacokinetics/pharmacodynamics (PK/PD), efficacy, and safety of AMG 181 in subjects with active, mild to moderate ulcerative colitis—an initial assessment. Gastroenterology 2013;144. S-230. Abstract SA1207.
15. Pan WJ, Sullivan BA, Rees WA, et al. Clinical pharmacology and safety of AMG 181, a human anti-$\alpha\beta$ antibody for treating inflammatory bowel disease. United European Gastroenterol J 2013;1. Abstract P914.
16. Pan WJ, Köck K, Rees WA, et al. Clinical pharmacology of AMG 181, a gut-specific human anti-$\alpha 4\beta 7$ monoclonal antibody, for treating inflammatory bowel diseases. Br J Clin Pharmacol 2014;78:1315–1333.
17. Dmitrienko A, D'Agostino RB Sr, Huque MF. Key multiplicity issues in clinical drug development. Stat Med 2013;32:1079–1111.
18. Meenan J, Spaans J, Grool TA, et al. Altered expression of alpha 4 beta 7, a gut homing integrin, by circulating and mucosal T cells in colonic mucosal inflammation. Gut 1997;40:241–246.
19. Yu Z, Sullivan BA, Rees WA, et al. Pharmacokinetics (PK), pharmacodynamics (PD), and safety profile of AMG 181 (MEDI7183) in healthy Japanese are not different from Caucasian subjects. Presented at: Annual Meeting of the American College of Clinical Pharmacology; 2013.
20. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med 2005;352:2499–2507.
21. Feagan BG, Rutgeerts PJ, Sands BE, et al. 943b Induction therapy for ulcerative colitis: results of GEMINI I, a randomized, placebo-controlled, double-blind, multicenter phase 3 trial. Gastroenterology 2012;142:S160–S161.
22. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet 2014;384:309–318.

Received April 2, 2018. Accepted November 17, 2018.

Reprint requests
Address requests for reprint to: William J. Sandborn, MD, Professor of Medicine and Adjunct Professor of Surgery, Chief of Division of Gastroenterology, Vice Chair for Clinical Operations, Department of Medicine, Director of UCSD IBD Center, University of California San Diego and UC San Diego Health System, 9500 Gilman Drive, MC 0956, La Jolla, California 92093. e-mail: wsandborn@ucsd.edu.

Conflicts of interest
William J. Sandborn has received research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, and Celgene/Receptos; has served as a consultant for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Conatus, Cosmo, Escalier Biosciences, Ferring, Genentech, Gilead, Janssen, Lilly, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Ritter Pharmaceuticals, Robarts Clinical Trials, Salix, Shire, Seres Therapeutics, Sigmoid Biotechnologies, Takeda, Tigenix, Tillotts Pharma, UCB Pharma, and Vivelix; and is a stockholder of Ritter Pharmaceuticals, Oppilan Pharma, Escalier Biosciences, Precision IBD, and Progenity. Marcoli Cyrille, Martha L. Cruz, Jun Yang, Michael J. Boedigheimer, Lubna Abuqayyas, and Christine M. Evangelista are employees and stockholders of Amgen Inc. Mark Berner Hansen is an employee of Zealand Pharma and a consultant for Bispebjerg Hospital. Brian G. Feagan has received research grants from AbbVie Inc, Amgen Inc, AstraZeneca/MedImmune Ltd, Atlantic Pharmaceuticals Ltd, Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech Inc/Hoffmann-La Roche Ltd, Gilead Sciences Inc, GlaxoSmithKline, Janssen Research & Development LLC, Pfizer Inc, Receptos Inc/Celgene International, Sanofi, Santarus Inc, Takeda Development Center Americas Inc, Tillotts Pharma AG, and UCB; has served as a consultant for Abbott/AbbVie, Ablynx, Akebia Therapeutics, Allergan, Amgen, Applied Molecular Transport Inc, AstraZeneca, Atlantic Pharma, Avir Pharma, Baxter Healthcare Corp, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, Galapagos, GiCare Pharma, Gilead, Given Imaging Inc, GSK, Inception IBD Inc, Ironwood Pharma, Janssen Biotech (Centocor), Johnson & Johnson/Janssen, Kyowa Kakko Kirin Co Ltd, Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestles, Nextbiotix, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Receptos, Roche/Genentech, Salix Pharma, Serano, Shire, Sigmoid Pharma, Synergy Pharma Inc, Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Vivelix Pharma, VHsquared Ltd, Warner-Chilcott, Wyeth, Zealand, and Zyngenia; is an officer of Robarts Clinical Trials Inc, Western University, London, Ontario, Canada; has served on the speaker's bureau for Abbott/AbbVie, Johnson & Johnson/Janssen, Lilly, Takeda, Tillotts, and UCB Pharma; and is an employee of the Western University Department of Medicine. Edward V. Loftus Jr has received research grants from AbbVie, UCB, Takeda, Janssen, Pfizer, Amgen, Genentech, Receptos, Celgene, Gilead, Robarts Clinical Trials, MedImmune, Allergan, and Seres Therapeutics; has served as a consultant for AbbVie, UCB, Takeda, Janssen, Pfizer, Amgen, Celgene, Eli Lilly, CVS Caremark, Celltrion Healthcare, and Napo Pharmaceuticals; and is the Co-Chief Medical Editor for *Healio Gastroenterology* (SLACK Incorporated). Gerhard Rogler has received research grants from Abbvie, Ardeypharm, Augurix, Calypso, Essex/MSD, FALK, Flamentera, Janssen, Novartis, Pfizer, Roche, Takeda, Tillots, UCB, and Zeller; is an owner/partner of PharmaBiome; has served as a consultant for Abbvie, Augurix, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Essex/MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions, and Zeller; has served on the speaker's bureau for AstraZeneca, Abbott, Abbvie, FALK, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, and Vifor; and is a stockholder of Nestle, Novartis, and Roche. Severine Vermeire has served as consultant for AbbVie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer Inc, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen; and has served on the speaker's bureau for AbbVie, MSD, Takeda, Ferring, Dr Falk Pharma, Hospira, Pfizer Inc, and Tillot. Barbara A. Sullivan is a former employee and stockholder of Amgen Inc. Walter Reinisch has served as a consultant for Abbvie, Aesca, Amgen, AM Pharma, AOP Orphan, Astellas, AstraZeneca, Avaxia, Roland Berger GmBH, Bioclinica, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, Elan, Eli Lilly, Ernest & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, Parexel, PDL, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical,

Sigmoid, Takeda, Therakos, Tigenix, UCB, Vifor, Zealand, Zyngenia, and 4SC; and has served on the speaker's bureau for Abbvie, Aesca, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult.

Funding
Financial support for this study was provided by Amgen and AstraZeneca/MedImmune.

Author contributions: The study concept and design were developed by William J. Sandborn, Brian G. Feagan, Edward V. Loftus Jr, Martha L. Cruz, and Walter Reinisch in collaboration with the study sponsor, Amgen. William J. Sandborn, Marcoli Cyrille, Brian G. Feagan, Edward V. Loftus Jr, Gerhard Rogler, Severine Vermeire, Christine M. Evangelista, and Barbara A. Sullivan contributed to the acquisition of data. William J. Sandborn, Marcoli Cyrille, Mark Berner Hansen, Brian G. Feagan, Edward V. Loftus Jr, Gerhard Rogler, Severine Vermeire, Jun Yang, Michael J. Boedigheimer, Lubna Abuqayyas, Christine M. Evangelista, Barbara A. Sullivan, and Walter Reinisch contributed to the analysis and interpretation of data in collaboration with the study sponsor, Amgen. All authors had full access to all data in the study and have critically reviewed the article for important intellectual content.

Writing assistance: was provided by Jessica Ma (Amgen Inc) and Fishawack Communications Inc (on behalf of Amgen Inc).

Methods

Study Design

Based on the healthy volunteer studies, dose levels of 7 mg, 21 mg, and 70 mg were selected because they were expected to achieve $\alpha_4\beta_7$ integrin occupancy in peripheral blood at or above 90%, 99%, and 99.9%, respectively, through 24 weeks of treatment. The 7-mg dose was selected to be "minimally efficacious" compared with the higher doses. The assumptions were that pharmacokinetic (PK) profiles observed in patients with inflammatory bowel disease would be similar to those of healthy volunteers, receptor occupancy measured in healthy volunteers generally would be predictive of receptor occupancy measured in patients with inflammatory bowel disease, and efficacy would be correlated with sustained receptor occupancy, as observed in the vedolizumab trials.

Pharmacokinetic and Pharmacodynamic Assessments

The PK bioanalytical assay to determine abrilumab serum concentration has been described previously.[15,16] Briefly, serum abrilumab concentrations were determined with a validated immunoassay using the Meso Scale Discovery (Gaithersburg, MD) electro-chemiluminescence platform with a lower limit of quantification of 10 ng/mL. Selectivity and extent of interference testing were used to address any endogenous molecules that could have caused matrix interference.

Noncompartmental analysis of abrilumab serum concentration data was performed using Phoenix WinNonlin 6.4 software on a Citrix (Pharsight Corp, St Louis, MO) as part of the validated PKS system on individual serum abrilumab concentrations to estimate the following PK parameters: maximum observed concentration achieved in plasma after dose administration, time to maximum observed concentration, and area under the concentration–time curve estimated using the linear trapezoidal method. Actual doses administered and actual sampling times were used in the noncompartmental analysis. Concentrations below a lower limit of quantification—10.0 ng/mL—were set to 0 before data analysis.

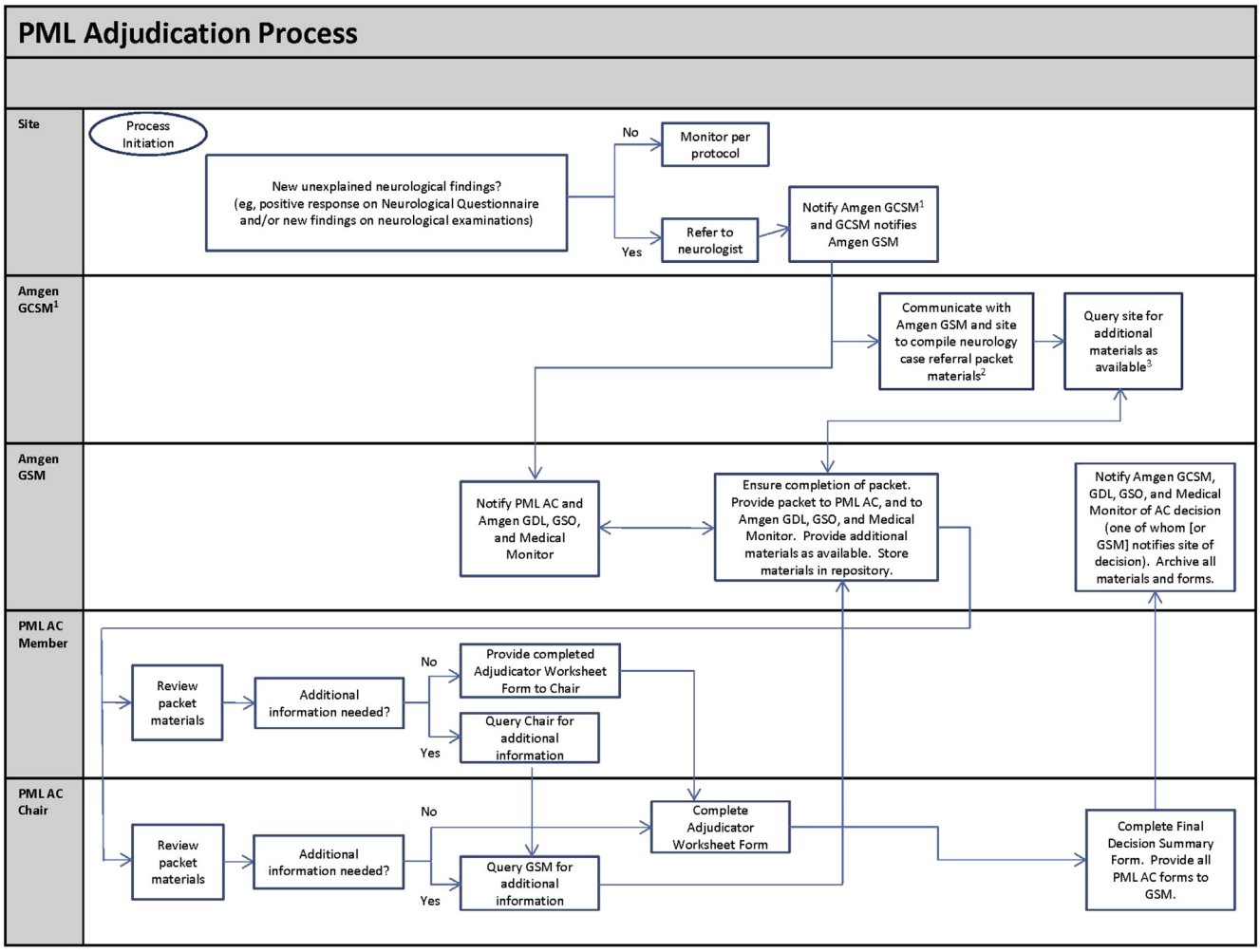
Flow Cytometry

Receptor occupancy was measured for whole-blood specimens from a sub-study of 129 patients by the Immunophenotyping and Absolute Counting assay, a validated semiquantitative flow cytometric assay. This assay was a simplified version of the abrilumab receptor occupancy assay described previously.[15] Briefly, a fluorochrome-labeled competing anti-$\alpha_4\beta_7$ antibody (anti-$\alpha_4\beta_7$–ROA1) was used to measure free $\alpha_4\beta_7$ levels, and a second fluorochrome-labeled noncompeting anti-β_7 antibody (anti-$\alpha_4\beta_7$–ROA2) was used to measure total $\alpha_4\beta_7$ receptor levels on T cells in peripheral blood. Although αE integrin is not frequently recorded in peripheral blood, an antibody recognizing the αE integrin was included in the flow cytometry panel to exclude $\alpha E\beta 7^+$ T cells from the receptor occupancy analysis by electronic gating.

Cells were gated on $CD45^+$ lymphocytes, $CD3^+$ T cells, and $CD8^-$ (as a surrogate for the $CD4^+$ T-cell population) and $CD103^-$ (αE^-) populations. Naïve $CD4^+$ T cells were further defined as $CCR7^+$ $CD45RA^+$ and assessed in this assay because abrilumab and anti-$\alpha_4\beta_7$–ROA1 bound the active and inactive forms of $\alpha_4\beta_7$ on naïve and memory $CD4^+$ T cells, with similar in vitro titration results. Naïve $CD4^+$ T cells expressed a single homogenous $\alpha_4\beta_7$ peak that allowed for continuous monitoring of the level of $\alpha_4\beta_7$ without interference of an $\alpha_4\beta_7^-$ peak. Baseline levels also were analyzed for their ability to predict clinical outcomes at week 8.

Absolute lymphocyte counts were determined using a 6-color TBNK reagent with Trucount tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) for enumeration of $CD3^+$ T cells, $CD3^+CD4^+$ T cells, $CD3^+CD8^+$ T cells, $CD16^+56^+$ natural killer cells, and $CD19^+$ B cells. Absolute counts of $CD4^+$ T-cell subsets were calculated by multiplying the percentage of the subset by the absolute count of the parent to generate a "relative-absolute" count. $CD4^+$ T cell subsets included memory $CD4^+$ T cells (identified as $CD45^+$ $CD3^+$ $CD8^-$ $CD103^-$ $CD45RA^-$) and central memory $CD4^+$ T cells (identified as $CD45^+$ $CD3^+$ $CD8^-$ $CD103^-$ $CD45RA^-$ $CCR7^+$).

Appendix A. Neurology Case Referral Adjudication Process Flowchart



GCSM, Global Clinical Site Management; GDL, Global Development Leader; GSM, Global Study Management; GSO, Global Safety Officer; PML AC, Progressive Multifocal Leukoencephalopathy Adjudication Committee.

[1]Amgen GCSM includes a Country Operations Manager and a Clinical Research Associate.

Appendix B. Case Adjudication Methodology—Case Definition

This appendix outlines the case definition for PML, adapted from joint European Medicines Agency and US Food and Drug Administration workshop (Transatlantic Workshop: Drug-Related Progressive Multifocal Leukoencephalopathy; July 25–26, 2011) with input from the Progressive Multifocal Leukoencephalopathy Adjudication Committee.

Characteristic brain biopsy (evidence of PML from brain biopsy examination): brain biopsy result with the classic histopathologic triad of PML (histopathologic demyelination, enlarged oligodendroglial cells, bizarre astrocytes) in addition to immunohistochemistry (John Cunningham [JC] virus T antigen and JC virus VP1 capsid protein) or in situ polymerase chain reaction (JC virus DNA) or electron microscopy (JC virions)

Clinical description (signs and symptoms compatible with PML): presence of focal neurologic deficits, including new deficits, that can be subacute in onset, or worsening deficits; with symptoms that can include behavior or personality changes, cognitive dysfunction, hemiparesis, language disturbance, retrochiasmal visual field defects, or new-onset seizures (a single symptom is sufficient to raise the question of PML)

Level 1: Characteristic brain biopsy result OR clinical description AND characteristic brain magnetic resonance imaging (MRI) AND positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) test result for JC virus DNA

Level 2: Clinical description AND characteristic brain MRI OR clinical description AND positive CSF PCR test result for JC virus DNA OR clinical description unclear or not reported but characteristic brain MRI AND positive CSF PCR test result for JC virus DNA

Level 3: Clinical description unclear or not reported AND brain MRI nonspecific or not reported but positive CSF PCR test result for JC virus AND immune reconstitution inflammatory syndrome after stopping immunosuppression

Level 4: Insufficient information AND not meeting exclusion criteria in Level 5

Level 5: Neurologic assessment leading to alternative diagnosis AND brain MRI not characteristic of PML, or negative CSF PCR test result for JC virus DNA, or brain biopsy result not characteristic of PML

Appendix C. PML Adjudication Worksheet Form

A **AMG 181**	Site No.	Subject ID No.

ADJUDICATION WORKSHEET FORM

This form captures the questions used for adjudication of PML. Please answer all questions.

Date of Form Completion by PML AC Member DD MMM YYYY			Event ID (provided by Amgen)

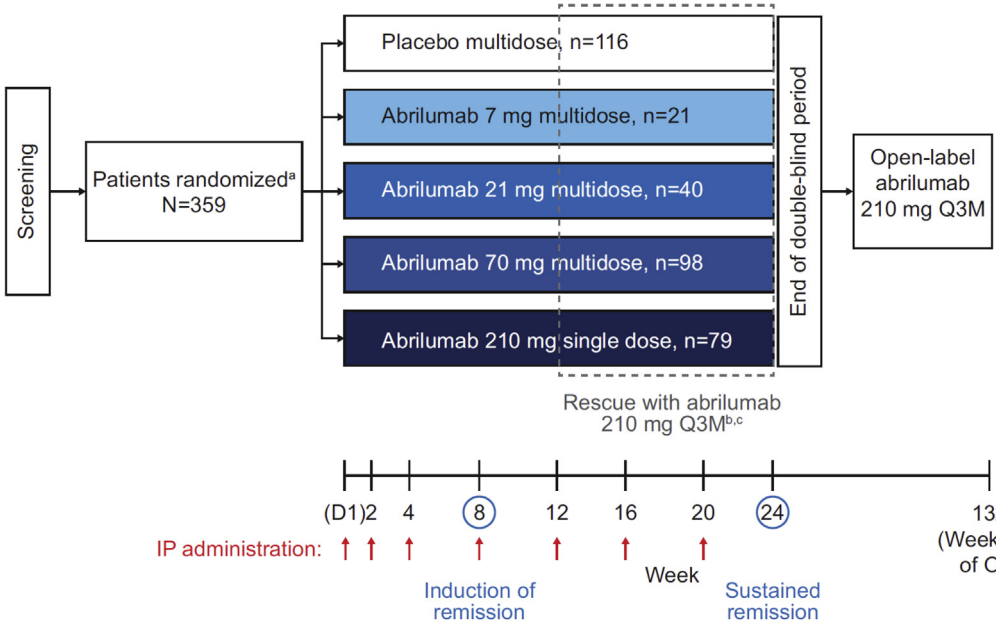
Based on the information received in the site packet, does this subject event meet the criteria to be a case of PML?	☐ PML ☐ Not consistent with PML ☐ Indeterminate
If you selected this to be a case of PML please state why? _____ _____	
If you did not select this to be a case of PML please state why? _____ _____	
Were the imaging information (eg, MRI films) of adequate quality to review and reach a decision?	☐Yes ☐No

Note: Please provide the completed form to the PML Adjudication Chair for completion of the final adjudication form using information above

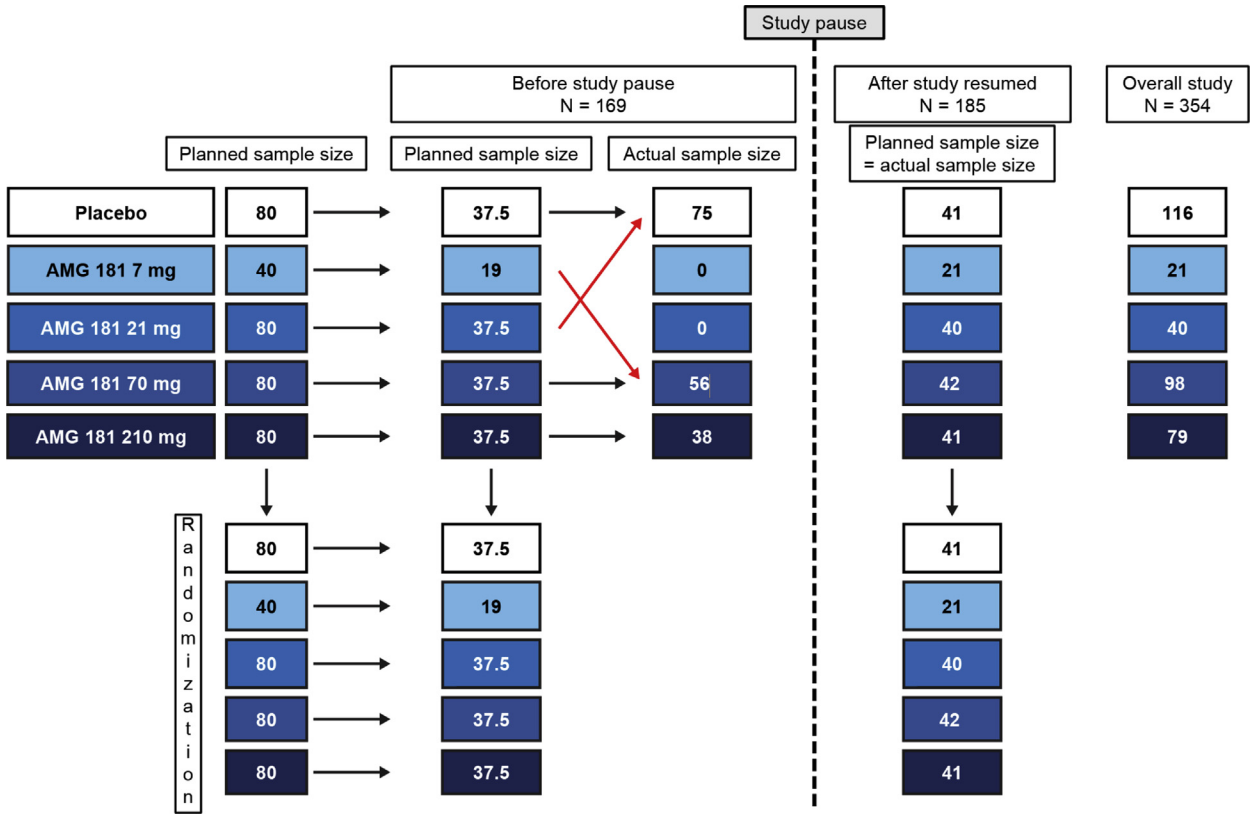
Name of PML AC Member:

Signature: _____ Date: _____

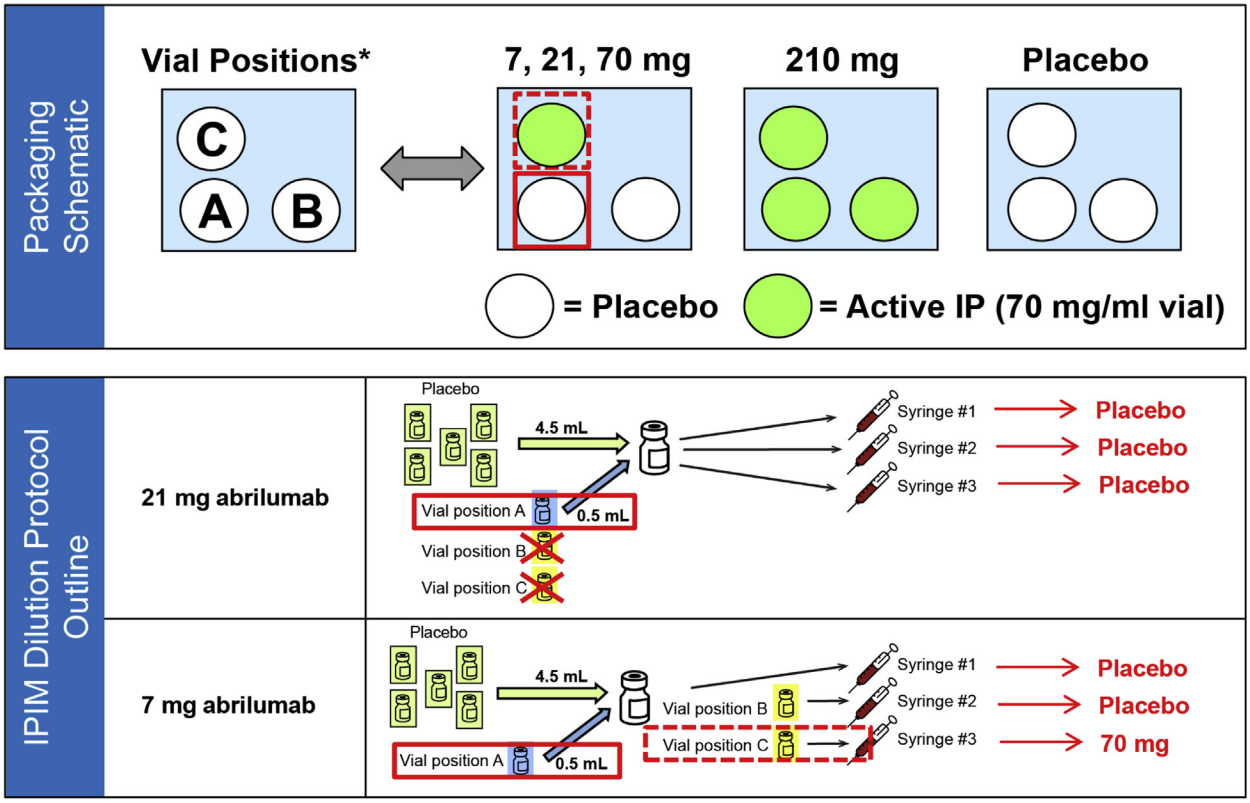
MRI, magnetic resonance imaging; PML AC, Progressive Multifocal Leukoencephalopathy Adjudication Committee.



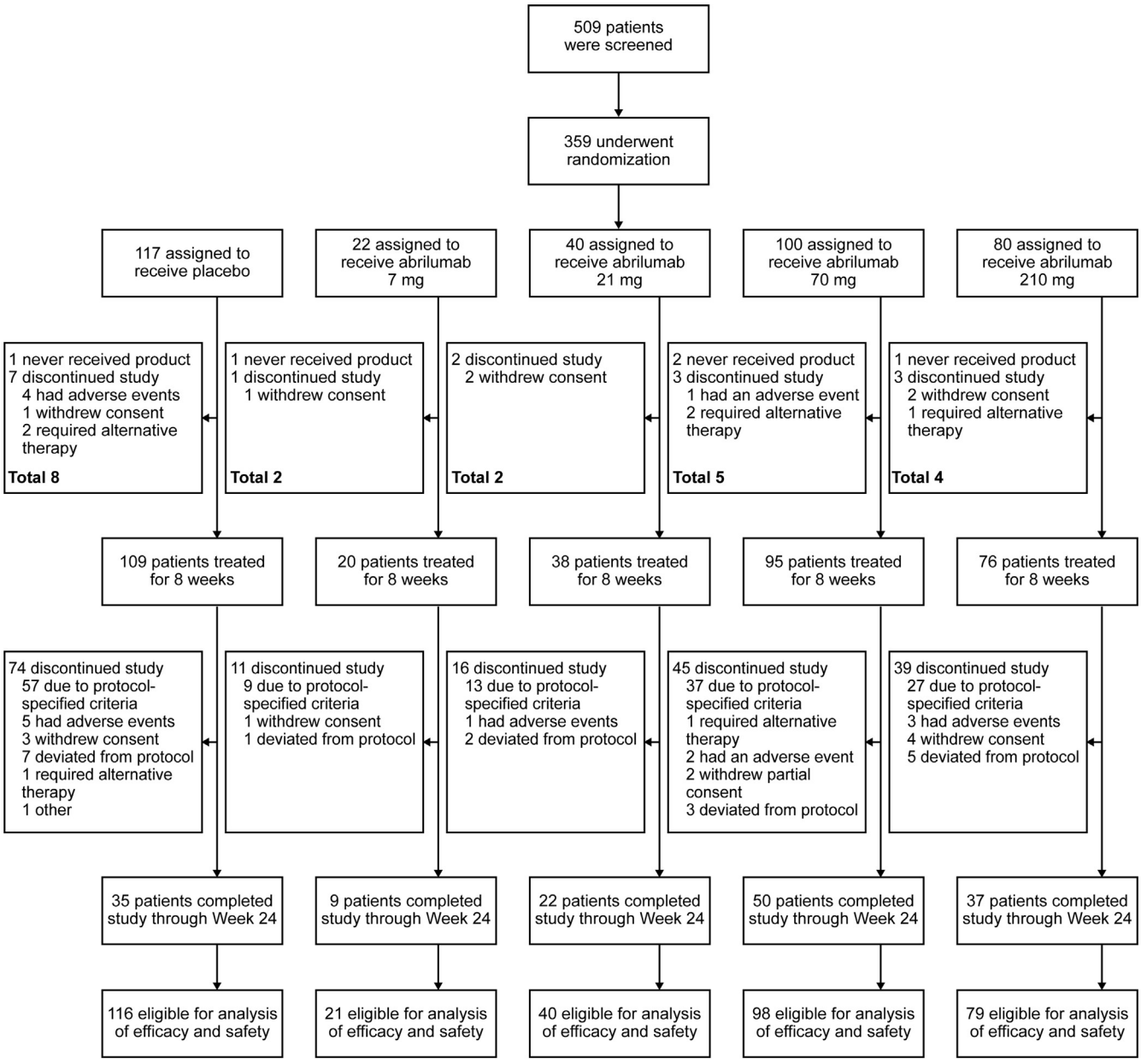
Supplementary Figure 1. Study design. Patients with moderate-to-severe UC were randomized to receive SC placebo or abrilumab at 7 mg, 21 mg, 70 mg (on day 1, week 2, week 4, and every 4 weeks thereafter until week 24) or 210 mg (a single dose on day 1 followed by placebo weeks 2 and 4 and every 4 weeks thereafter until week 24). [a]A systematic misalignment in IP resulted in a final allocation at a ratio different from that stipulated in the protocol. [b]Patients who did not achieve a response at week 8 and had an inadequate response at week 12 or after were eligible to enter the OL period early. [c]Patients who achieved a response and/or remission at week 8 and subsequently experienced disease worsening were eligible to enter the OL period early. D, day; OL, open-label; Q3M, every 3 months.



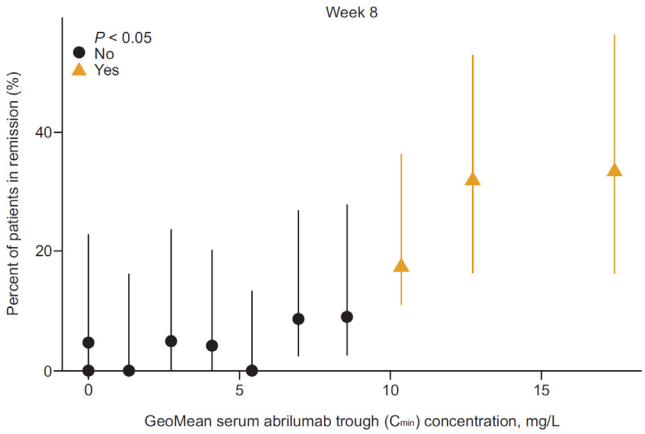
Supplementary Figure 2. Systematic misalignment of treatment allocation in study. Owing to a systematic misalignment, all patients who were randomized to receive 7 mg actually received 70 mg and all patients who were randomized to receive 21 mg actually received placebo before the study was paused.



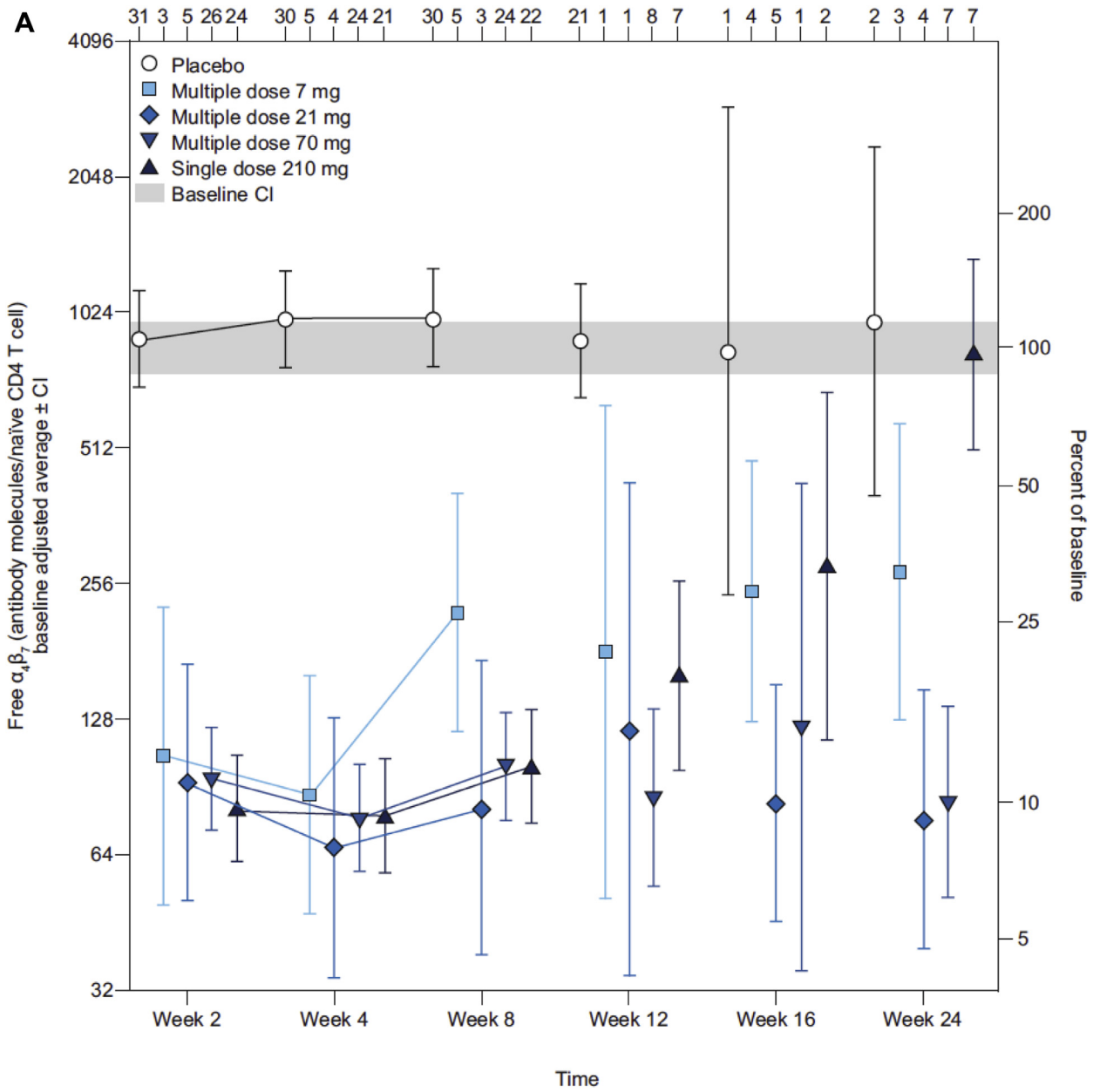
Supplementary Figure 3. Systematic misalignment by IPIM vs active vial positions before study pause. *Primary label does contain the text "A," "B," and "C." A systematic misalignment in IP dosing before study pause occurred because of a misalignment in the IPIM compared with the active vial positions in the package. Although the IPIM protocol identified "Vial Position A" as the active IP (ie, abrilumab), in the actual package, the IP was in "Vial Position C." The placebo, 70-mg, and 210-mg treatment arms did not require dilution; the 21- and 7-mg treatment arms did require dilution. Dosing required 3 injections—3 syringes with 1 mL each. When 0.5 mL of vial A was diluted into placebo 4.5 mL for the 7-mg arm (*lower row of bottom panel*), placebo was diluted into placebo; this vial was used to fill syringe 1 (placebo). Vials B and C were used to fill the 2 additional syringes (syringes 2 and 3, placebo and abrilumab 70 mg/mL, respectively). Each patient received all 3 injections and therefore patients planned to receive abrilumab 7 mg actually received 70 mg. For the 21-mg arm (*upper row of bottom panel*), 3 syringes were filled from a master vial that was created by diluting 0.5 mL of vial A into placebo 4.5 mL, which was placebo diluted into placebo. Each patient received all 3 injections and therefore patients planned to receive abrilumab 21 mg actually received placebo. Together, these resulted in the mis-dosing of patients randomized to the 7-mg dose to receive 70 mg and the 21-mg dose to receive placebo. This misalignment in vial positions described was at the root of mis-dosing in the 7- and 21-mg treatment arms. The Interactive Voice Response System/Interactive Web Response System used for randomization was not implicated.



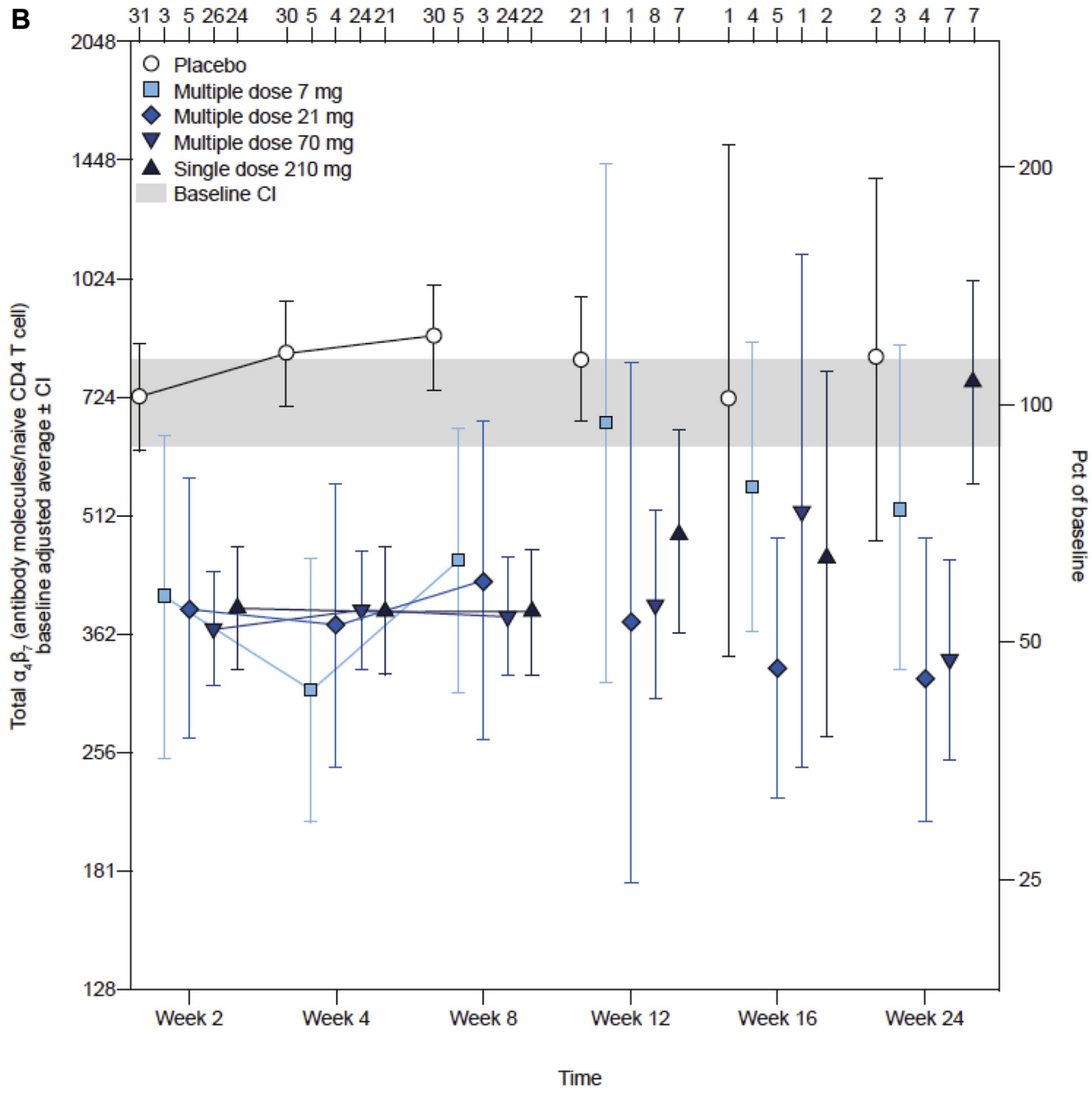
Supplementary Figure 4. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Patients with moderate-to-severe UC were randomized to receive SC placebo (n = 117), abrilumab 7 mg (n = 22), 21 mg (n = 40), 70 mg (n = 100), and 210 mg (n = 80). Efficacy and safety populations through week 24 consisted of 354 randomized patients who received ≥1 dose of IP.



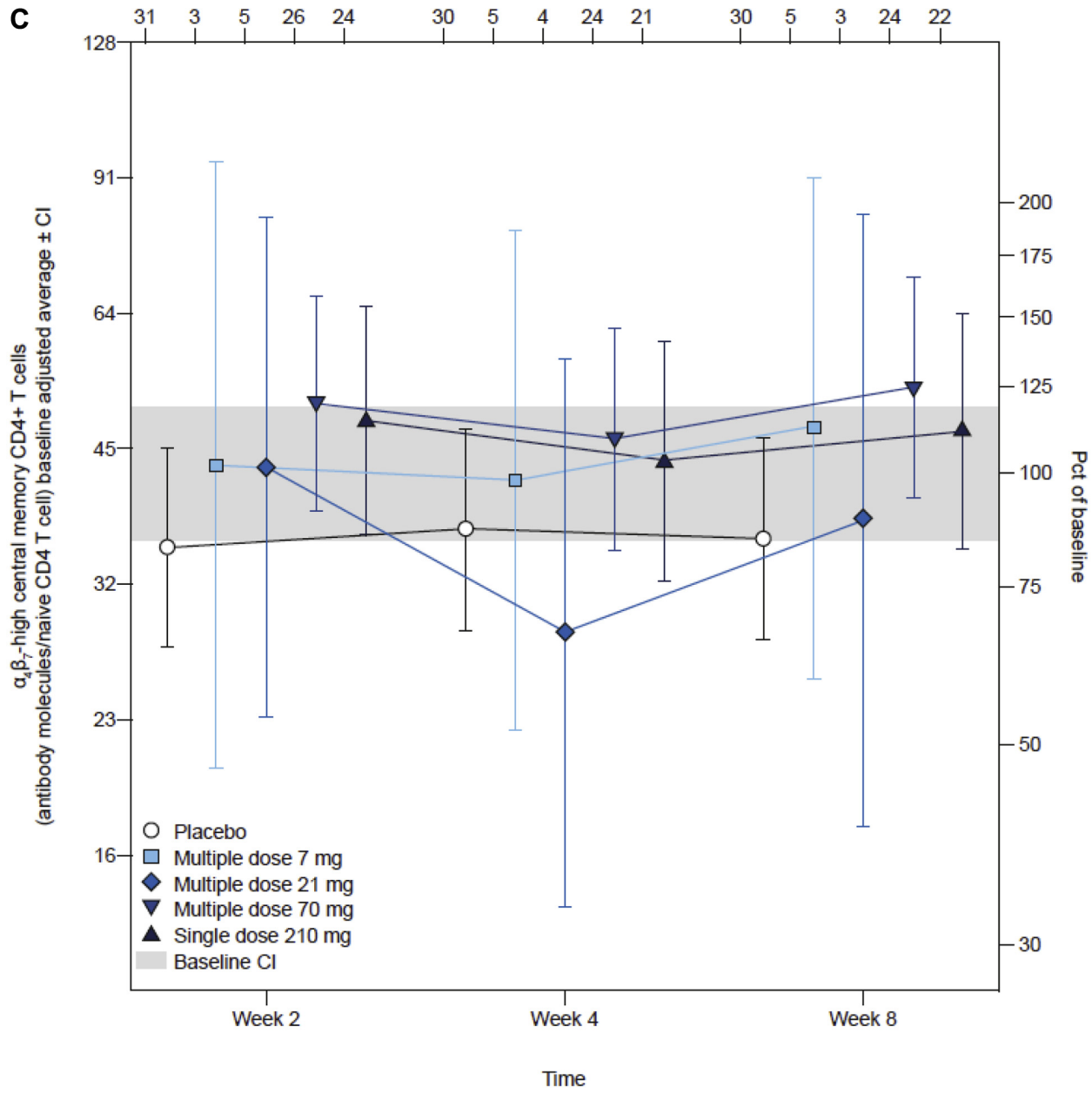
Supplementary Figure 5. Exposure–response analysis of percentage of patients in remission compared with abrilumab trough concentration. Fraction of patients in remission at week 8 by trough serum abrilumab concentration (C_{min}) decile. A *P* value $<.05$ for a decile indicates that the remission rate in that decile is significantly different than placebo. Logistic regression showed that C_{min} was the best exposure metric to describe remission status at week 8. Error bars represent 95% CI around the mean for that decile group. C_{min}, minimum blood plasma concentration; GeoMean, geometric mean.



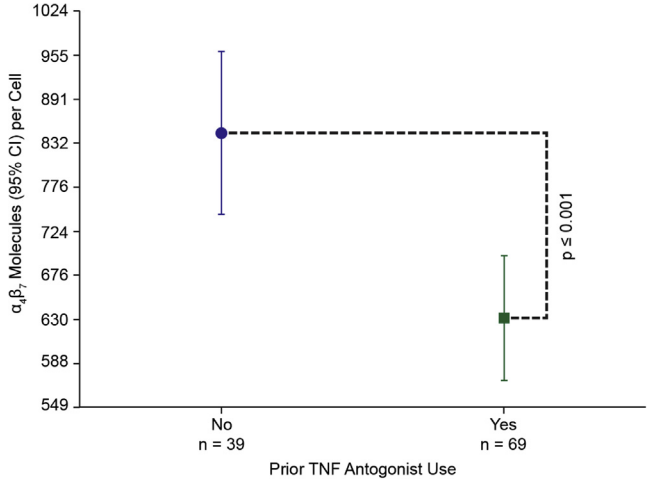
Supplementary Figure 6. Pharmacodynamic effect of abrilumab on $\alpha_4\beta_7$. Average (± 95% CI) baseline-normalized (*A*) free $\alpha_4\beta_7$ receptor profiles on $CD4^+$-naïve T cells, (*B*) total $\alpha_4\beta_7$ receptor profiles on $CD4^+$-naïve T cells, and (*C*) $\alpha_4\beta_7^{hi}$ central memory $CD4^+$ T cells after abrilumab administration in patients with UC. A single measurement of immunophenotyping receptor occupancy with absolute counts was performed for patients entering the open-label trial at week 12, 16, or 24. Values at week 16 were entirely missing for the 7-mg and 21-mg groups and were imputed from the adjacent visits to allow the model to be fit without meaningfully affecting the interpretation of the plot. The number of patients per treatment group by visit is shown at the top of the plot, with the exception of imputed values.



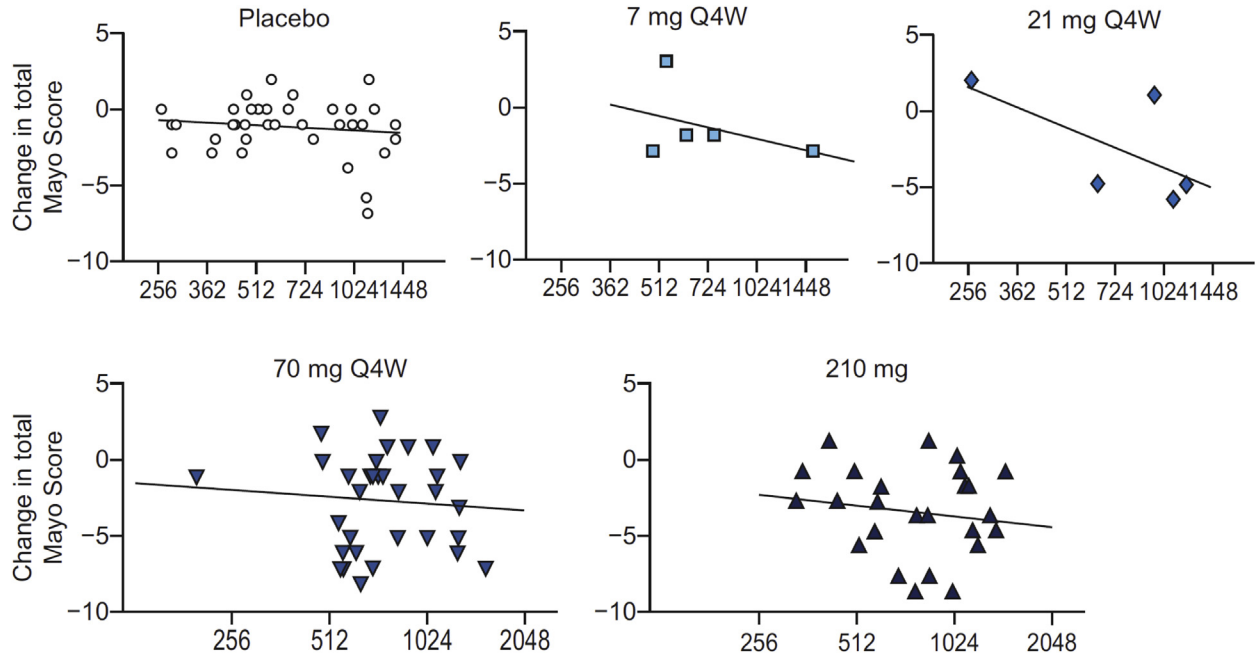
Supplementary Figure 6. (*continued*).



Supplementary Figure 6. (*continued*).



Supplementary Figure 7. Relation between baseline levels of $\alpha_4\beta_7$ and prior TNF antagonist use. Geometric mean baseline $\alpha_4\beta_7$ levels per cell in patients with and without prior TNF antagonist use were calculated using a linear model of log-transformed data. 95% CIs and contrasts between groups were performed. Means and intervals were back-transformed for display.



Supplementary Figure 8. Relation between baseline levels of $\alpha_4\beta_7$ on $CD4^+$-naïve T cells and change in total Mayo Score at week 8. Baseline levels of $\alpha_4\beta_7$ on $CD4^+$-naïve T cells and change in Mayo Score at week 8 were analyzed to determine the ability of $\alpha_4\beta_7$ levels to predict clinical outcomes. Each panel shows an individual dose group and the best-fit linear regression line for the 2 variables. Q4W, every 4 weeks.

Supplementary Table 1. Summary of Response at Week 8

		Abrilumab			
	Placebo	7 mg Q4W	21 mg Q4W	70 mg Q4W	210 mg
All patients, N	116	21	40	98	79
Non-adjusted response rate using NRI, n (%)	30 (25.9)	3 (14.3)	20 (50.0)	48 (49.0)	37 (46.8)
Adjusted response rate using NRI, %	26.0	12.3	47.2	49.4	47.4
Difference, % (90% CI)	—	−13.7 (−24.4 to 2.7)	21.2 (4.9–34.1)	23.4 (11.8–33.2)	21.4 (9.0–31.8)
OR (90% CI)		0.40 (0.13–1.22)	2.54 (1.29–5.02)	2.78 (1.71–4.52)	2.57 (1.53–4.31)
P value		.18	.024	<.001	.003
Patients with TNF antagonist failure, n	70	5	10	50	38
Non-adjusted response rate using NRI, n (%)	20 (28.6)	1 (20.0)	3 (30.0)	22 (44.0)	20 (52.6)
Adjusted response rate using NRI, %	27.1	21.3	31.7	41.1	51.9
Difference, % (90% CI)	—	−5.8 (−26.4 to 36.3)	4.6 (−26.8 to 24.7)	14.0 (−2.1 to 26.7)	24.8 (6.9–38.7)
OR (90% CI)		0.73 (0.10–5.32)	1.25 (0.32–4.93)	1.88 (0.98–3.59)	2.91 (1.45–5.84)
P value		.79	.79	.11	.012
Patients naïve to TNF antagonist	44	16	30	43	41
Non-adjusted response rate using NRI, n (%)	10 (22.7)	2 (12.5)	17 (56.7)	23 (53.5)	17 (41.5)
Adjusted response rate using NRI, %	17.7	6.9	42.9	49.8	34.7
Difference, % (90% CI)	—	−10.8 (−20.6 to 7.5)	25.2 (4.8–40.1)	32.1 (14.1–45.5)	17.0 (−0.8 to 30.1)
OR (90% CI)		0.34 (0.09–1.40)	3.50 (1.46–8.38)	4.61 (2.03–10.50)	2.47 (1.10–5.59)
P value		.21	.018	.002	.067

NOTE. Response at week 8 was defined as a decrease from baseline in total Mayo Score of ≥3 points and ≥30% decrease from baseline, with an accompanying decrease in the sub-score for rectal bleeding of ≥1 point or the absolute sub-score for rectal bleeding of 0 or 1.
N, number of patients in full analysis set; n, number of patients who reached response status at week 8; Q4W, every 4 weeks.

Supplementary Table 2. Summary of Mucosal Healing at Week 8

		Abrilumab			
	Placebo	7 mg Q4W	21 mg Q4W	70 mg Q4W	210 mg
All patients, N	116	21	40	98	79
Non-adjusted mucosal healing rate using NRI, n (%)	25 (21.6)	3 (14.3)	6 (15.0)	32 (32.7)	23 (29.1)
Adjusted mucosal healing rate using NRI, %	16.8	12.2	13.9	32.2	29.8
Difference, % (90% CI)	—	−4.6 (−14.9 to 11.3)	−3.0 (−11.9 to 9.4)	15.3 (4.8–24.0)	13.0 (1.7–22.1)
OR (90% CI)		0.69 (0.21–2.22)	0.80 (0.32–1.97)	2.34 (1.35–4.07)	2.10 (1.15–3.82)
P value		.60	.68	.011	.041
Patients with TNF antagonist failure, n	70	5	10	50	38
Non-adjusted mucosal healing rate using NRI, n (%)	16 (22.9)	0	1 (10)	13 (26.0)	15 (39.5)
Adjusted mucosal healing rate using NRI, %	16.0	10.6	13.2	18.8	40.6
Difference, % (90% CI)	—	−5.4 (−18.4 to 29.1)	−2.8 (−16.1 to 22.0)	2.8 (−10.5 to 12.7)	24.6 (7.6–37.6)
OR (90% CI)		0.62 (0.03–12.34)	0.80 (0.13–5.10)	1.22 (0.57–2.58)	3.59 (1.60–8.08)
P value		.79	.84	.67	.009
Patients naïve to TNF antagonist, n	44	16	30	43	41
Non-adjusted mucosal healing rate using NRI, n (%)	9 (20.5)	3 (18.8)	5 (16.7)	17 (39.5)	8 (19.5)
Adjusted mucosal healing rate using NRI, %	11.7	9.9	10.8	43.3	13.8
Difference, % (90% CI)	—	−1.8 (−12.1 to 17.1)	−0.9 (−10.3 to 14.2)	31.7 (14.6–44.2)	2.1 (−12.1 to 11.7)
OR (90% CI)		0.83 (0.22–3.08)	0.91 (0.30–2.77)	5.80 (2.23–15.12)	1.21 (0.46–3.18)
P value		.82	.89	.003	.74

NOTE. Mucosal healing was defined as the absolute sub-score for recto-sigmoidoscopy of 0 or 1.
N, number of patients in full analysis set; n, number of patients who reached mucosal healing status at week 8; Q4W, every 4 weeks.

Supplementary Table 3. Summary of Remission at Week 24

All patients	Placebo (n = 116)	Abrilumab 7 mg Q4W (n = 21)	Abrilumab 21 mg Q4W (n = 40)	Abrilumab 70 mg Q4W (n = 98)	Abrilumab 210 mg (n = 79)
Non-adjusted remission rate using NRI, n (%)	14 (12.1)	2 (9.5)	7 (17.5)	22 (22.4)	10 (12.7)
Adjusted remission rate using NRI, (%)	12.5	7.0	13.8	22.9	12.4
Difference, % (90% CI)	—	−5.5 (−13.1 to 7.8)	1.3 (−10.7 to 9.9)	10.4 (0.9–18.1)	−0.1 (−7.0 to 8.9)
OR[a] vs placebo (90% CI)	—	0.53 (0.14–2.04)	1.12 (0.46–2.72)	2.08 (1.12–3.88)	0.99 (0.47–2.07)
P value[b]	—	.44	.83	.052	.98

N, number of patients in full analysis set; n, number of patients who reached remission status at week 24; Q4W, every 4 weeks.
[a]The OR and *P* value were obtained from a logistic regression model including the factors of treatment group, stratification factors (prior vs no prior TNF antagonist use and pre- vs post-protocol amendment 3) and baseline total Mayo Score, using NRI. An OR >1.0 indicates a higher remission rate for the abrilumab treatment group vs placebo.
[b]All *P* values are nominal.

Supplementary Table 4. Summary of Response at Week 24

All patients	Placebo (N = 116)	Abrilumab 7 mg Q4W (N = 21)	Abrilumab 21 mg Q4W (N = 40)	Abrilumab 70 mg Q4W (N = 98)	Abrilumab 210 mg (N = 79)
Non-adjusted response rate using NRI, n (%)	29 (25.0)	4 (19.0)	16 (40.0)	35 (35.7)	24 (30.4)
Adjusted response rate using NRI, (%)	25.8	16.4	36.4	36.3	30.3
Difference, % (90% CI)	—	−9.4 (−21.5, 8.2)	10.6 (−5.3 to 23.1)	10.5 (0.8–20.0)	4.5 (−7.4 to 14.2)
OR[a] vs placebo (90% CI)	—	0.56 (0.20–1.56)	1.64 (0.82–3.28)	1.64 (1.00–2.70)	1.25 (0.72–2.15)
P value[b]	—	0.35	0.24	0.10	0.50

N, number of patients in full analysis set; n, number of patients who reached response status at week 24; Q4W, every 4 weeks.
[a]The OR and *P* value were obtained from a logistic regression model including the factors of treatment group, stratification factors (prior vs no prior TNF antagonist use and pre- vs post-protocol amendment 3), and baseline total Mayo Score using NRI. An OR >1.0 indicates a higher remission rate for the abrilumab treatment group vs placebo.
[b]All *P* values are nominal.

Supplementary Table 5. Summary of Mucosal Healing at Week 24

All patients	Placebo (n = 116)	Abrilumab 7 mg Q4W (n = 21)	Abrilumab 21 mg Q4W (n = 40)	Abrilumab 70 mg Q4W (n = 98)	Abrilumab 210 mg (n = 79)
Non-adjusted healing rate using NRI, n (%)	22 (19.0)	4 (19.0)	15 (37.5)	33 (33.7)	19 (24.1)
Adjusted healing rate using NRI, (%)	18.2	14.9	32.5	34.7	24.1
Difference, % (90% CI)	—	−3.3 (−14.5 to 13.6)	14.3 (−0.9 to 26.1)	16.5 (5.7–25.4)	5.9 (−5.0 to 14.7)
OR[a] vs placebo (90% CI)	—	0.79 (0.28–2.23)	2.16 (1.04–4.48)	2.39 (1.39–4.10)	1.43 (0.78–2.61)
P value[b]	—	.71	.082	.008	.33

N, number of patients in full analysis set; n, number of patients who reached mucosal healing status at week 24; Q4W, every 4 weeks.
[a]The OR and *P* value were obtained from a logistic regression model including the factors of treatment group, stratification factors (prior vs no prior TNF antagonist use and pre- vs post-protocol amendment 3), and baseline recto-sigmoidoscopy score using NRI. An OR >1.0 indicates a higher remission rate for the abrilumab treatment group vs placebo.
[b]All *P* values are nominal.

Supplementary Table 6. Summary of Sustained Remission at Weeks 8 and 24

All patients	Placebo (n = 116)	Abrilumab 7 mg Q4W (n = 21)	Abrilumab 21 mg Q4W (n = 40)	Abrilumab 70 mg Q4W (n = 98)	Abrilumab 210 mg (n = 79)
Observed remission rate, n/N1 (%)	3/32 (9.4)	0/8 (0.0)	1/22 (4.5)	8/46 (17.4)	3/32 (9.4)
Non-adjusted remission rate using NRI, n/N (%)	3/116 (2.6)	0/21 (0.0)	1/40 (2.5)	8/98 (8.2)	3/79 (3.8)
Difference, % (90% CI)		−2.6 (−5.0 to −0.2)	−0.1 (−4.8 to 4.6)	5.6 (0.4–10.7)	1.2 (−3.1 to 5.5)

N, number of patients in analysis set; n, number of patients who reached remission status at weeks 8 and 24 (ie, sustained remission); N1, number of patients with total Mayo Score at weeks 8 and 24; Q4W, every 4 weeks.

Supplementary Table 7. Summary of Corticosteroid-Free Remission at Week 24

		Abrilumab			
All patients	Placebo (n = 116)	7 mg Q4W (n = 21)	21 mg Q4W (n = 40)	70 mg Q4W (n = 98)	210 mg (n = 79)
Observed remission rate, n/N1 (%)	5/32 (15.6)	0/8 (0.0)	3/22 (13.6)	7/46 (15.2)	4/32 (12.5)
Non-adjusted healing rate using NRI, n/N (%)	5/116 (4.3)	0/21 (0.0)	3/40 (7.5)	7/98 (7.1)	4/79 (5.1)
Difference, % (90% CI)		−4.3 (−7.4 to −1.2)	3.2 (−4.3 to 10.7)	2.8 (−2.5 to 8.1)	0.8 (−4.4 to 5.9)

N, number of patients in analysis set; n, number of patients who reached corticosteroid-free remission at week 24; N1, number of subjects with total Mayo Score at week 24; Q4W, every 4 weeks.

Supplementary Table 8. Mean (SD) PK Parameter Estimates After SC Administration of Abrilumab

Treatment group	t_{max} (d), median (IQR)	C_{max} (μg/mL)	AUC_{tau} (d · μg/mL)	AUC_{inf} (d · μg/mL)
7 mg (n = 3)	8.0 (6.7–13.9)	2.48 (3.06)	51.2 (65.7)	NR
21 mg (n = 5–6[a])	6.5 (0.0–14.8)	6.43 (2.80)	125 (54.6)	NR
70 mg (n = 5)	7.0 (6.7–13.9)	18.3 (9.08)	363 (197)	NR
210 mg (n = 4–9[b])	7.9 (6.8–14.0)	27.5 (10.4)	NR	610 (317)

NOTE. Data are mean (SD) unless otherwise noted.
AUC_{inf}, area under concentration–time curve from time 0 to infinity; AUC_{tau}, area under concentration–time curve during dosing interval tau (28 days); C_{max}, maximum observed concentration; t_{max}, time to maximum observed concentration; IQR, interquartile range; NR, not reported.
[a]N = 6 for C_{max} and t_{max}; n = 5 for AUC_{tau}.
[b]N = 9 for C_{max} and t_{max}; n = 4 for AUC_{inf}.

Supplementary Table 9. Mean (SD) Trough PK Concentrations (μg/mL) at Weeks 8 and 24

Treatment group	Week 8	Week 24
7 mg	0.482 (0.749)	0.471 (0.925)
21 mg	3.13 (1.95)	2.26 (1.73)
70 mg	10.5 (5.33)	11.5 (6.83)
210 mg	6.78 (3.65)	0.243 (0.817)

Supplementary Table 10. Change From Baseline CRP Concentration at Weeks 8 and 24

		Abrilumab			
All patients	Placebo (n = 116)	7 mg Q4W (n = 21)	21 mg Q4W (n = 40)	70 mg Q4W (n = 98)	210 mg (n = 79)
Week 8					
Mean change (SE)	−2.90 (1.75)	−4.10 (1.95)	0.54 (1.37)	−1.19 (1.13)	−1.11 (1.52)
LS mean change (90% CI)	−1.72 (−3.6 to 0.2)	−1.34 (−3.7 to 1.0)	0.29 (−2.0 to 2.5)	−2.51 (−4.1 to −1.0)	−0.78 (−2.8 to 1.2)
LS mean treatment difference (90% CI)	—	0.38 (−2.6 to 3.3)	2.01 (−0.8 to 4.8)	−0.79 (−3.3 to 1.7)	0.94 (−1.8 to 3.7)
P value	—	.83	.24	.60	.58
Week 24					
Mean change (SE)	−4.20 (2.18)	−2.36 (3.74)	3.18 (1.30)	0.18 (2.28)	−2.95 (3.02)
LS mean change (90% CI)	−4.72 (−6.6 to −2.8)	−2.17 (−7.2 to 2.9)	2.54 (−2.1 to 7.2)	−0.14 (−4.0 to 3.7)	−2.72 (−5.9 to 0.4)
LS mean treatment difference (90% CI)	—	2.55 (−2.8 to 7.9)	7.26 (2.2–12.3)	4.58 (0.1–9.0)	2.00 (−1.8 to 5.8)
P value	—	.44	.019	.091	.38

LS, least squares; Q4W, every 4 weeks; SE, standard error.

Supplementary Table 11. Change From Baseline FCP Concentration at Weeks 8 and 24

		Abrilumab			
All patients	Placebo (n = 116)	7 mg Q4W (n = 21)	21 mg Q4W (n = 40)	70 mg Q4W (n = 98)	210 mg (n = 79)
Week 8					
Mean change (SE)	−115.79 (283.67)	30.15 (339.27)	−440.98 (225.14)	−319.34 (338.08)	−354.52 (182.29)
LS mean change (90% CI)	65.63 (−318.7 to 450.0)	−198.29 (−1048.1 to 651.6)	−648.24 (−876.2 to −420.3)	−325.41 (−800.8 to 150)	−531.32 (−739.3 to −323.3)
LS mean treatment difference (90% CI)	—	−263.92 (−1224.8 to 697.0)	−713.88 (−1233.7 to −194.1)	−391.04 (−996.2 to 214.1)	−596.95 (−1032.8 to −161.1)
P value	—	.65	.024	.29	.024
Adjusted >50% decrease rate, using NRI	28.5	30.5	30.2	45.4	28.6
Treatment difference % (90% CI)		2.0 (−22.8 to 19.1)	1.7 (−15.9 to 15.1)	17.0 (3.6 to 27.9)	0.1 (−13.1 to 10.8)
OR[a] vs placebo (90% CI)		1.10 (0.39–3.12)	1.09 (0.48–2.44)	2.09 (1.19–3.66)	1.01 (0.55–1.85)
P value		.88	.87	.030	.98
Week 24					
Mean change (SE)	−1122.20 (442.48)	104.64 (612.83)	−663.62 (470.36)	−506.22 (295.00)	−326.50 (262.78)
LS mean change (90% CI)	−826.53 (−967.6 to −685.4)	162.88 (−990.5 to 1316.3)	−734.52 (−1114.6 to −354.5)	−612.60 (−790.4 to −434.8)	−515.08 (−766.8 to −263.3)
LS mean treatment difference (90% CI)	—	989.41 (−186.7 to 2165.5)	92.01 (−317.2 to 501.2)	213.93 (−9.8 to 437.6)	311.45 (23.5 to 599.4)
P value	—	.17	.71	.12	.075

LS, least squares; Q4W, every 4 weeks; SE, standard error.

[a]The OR and *P* value were obtained from a logistic regression model including the factors of treatment group, stratification factor (prior vs no prior TNF antagonist use and pre- vs post-protocol amendment 3), and baseline FCP value using NRI. An OR >1.0 indicates a higher >50% FCP decrease rate for the abrilumab treatment group vs placebo.